VOLUME 27 NUMBER 4

AMERICAN JOURNAL
OF
DISEASES OF CHILDREN

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APRIL, 1924

PUBLISHED MONTHLY BY THE AMERICAN MEDICAL ASSOCIATION
DEARBORN STATION, CHICAGO, ILLINOIS

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American Journal of Diseases of Children

VOL. 27 APRIL, 1924 NO. 4

STUDIES ON ANEMIA IN INFANCY: THE UROBILIN CONTENT OF THE STOOLS OF NORMAL INFANTS*

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During the past decade the problem of the anemias has been approached by new paths. Interest centers not so much in the morphology as in the physiology of the blood, the way the hematopoietic system performs its function. The function of the blood forming organs is to preserve the hemoglobin, and the red and white cells at a certain level. This stability is maintained by a balance between two opposing forces; the continuous destruction of blood cells is compensated by an equivalent regeneration.

There is no single criterion of blood regeneration. When the percentage of hemoglobin, and the number of red and white cells fall within normal limits, and there are no abnormal cells in the blood stream, blood regeneration may be considered normal. The presence in the circulation of immature cells reflects the degree of strain under which the bone marrow is working. Nucleated forms, normoblasts and megaloblasts, indicate a severe functional incapacity. An excessive number of reticulated cells indicates a lesser degree of injury. Reticulated cells are non-nucleated red cells that show a fine black skein or reticulum, or only black granulations, when vitally stained by such dyes as cresyl blue. In normal adult blood they form about 0.5 per cent. of the red cells and in the blood of infants a somewhat higher percentage. Though still immature, they are more nearly completely developed than are the nucleated red cells. Their presence in excess indicates that the bone marrow is responding well to demands made on it by the production of cells closely approaching normal. Thus, one function of the blood forming organs, blood regeneration,

* Received for publication, Jan. 21, 1924.

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may be gauged by the number of red and white cells, the percentage of hemoglobin and the presence and number of immature and abnormal forms.[1]

To determine the degree of blood destruction we have relied on the estimation of the amount of urobilin and urobilinogen in the feces. The association of urobilin with the fate of hemoglobin is illustrated in Table 1. This conception in its entirety is not universally accepted.

TABLE 1.—*The Association of Urobilinogen with the Fate of Hemoglobin*

Liver	Bile Passages	Intestine	Portal Stream	Liver
Hemoglobin—Hemochromogen—(Globin, Iron salt)	Bilirubin—	part destroyed Urobilin—— *part excreted	Urobilin—	Bilirubin-Hemoglobin?

* Only this portion of the urobilin, the amount excreted in the feces, can be estimated.

According to Whipple, urobilin may be synthesized by the liver cells and Whipple also questions the reabsorption of bile pigments from the intestine, the classical theory of "the circulation of the bile." [2] In addition, adventitious circumstances, mentioned under technic, affect the quantitative accuracy of the method of estimating urobilin devised by Wilbur and Addis and used in the present work. Nevertheless, urobilin estimation is a sufficiently accurate indicator of the degree of blood destruction for clinical work.

The final purpose of this work is to determine the rôle of excessive blood destruction in certain of the anemias of infancy. Possibly the anemias of infancy might fall naturally into certain groups, depending on whether there is excessive blood destruction, inadequate regeneration or both. Preliminary to such studies it was necessary to determine the urobilin output in the stools of normal infants, or rather of infants whose hemoglobin fell within normal limits, and who were not suffering from any acute disease.

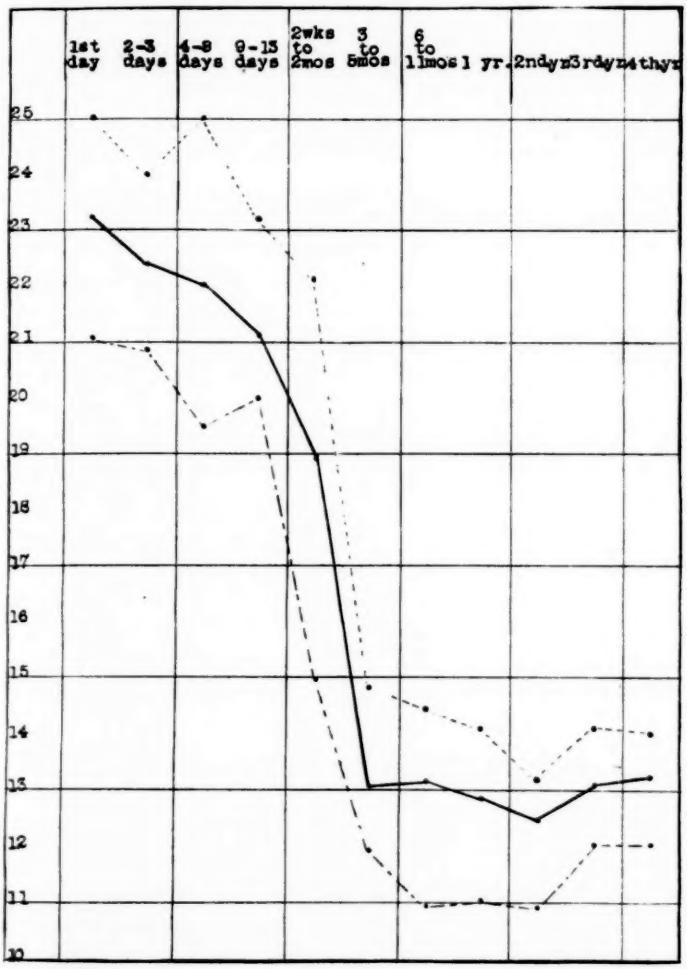
Normal hemoglobin values are subject to wide variations in infancy. Williamson [3] demonstrated this in very striking manner by the estimation of the hemoglobin of normal individuals with the spectrophotometer. The chart, taken from his work, presents the hemoglobin values for children under 4 years of age. The variation depending on age is

1. There are other criteria of blood regeneration. Hurwitz, in Metabolism and Endocrinology, Vol. 4, New York, D. Appleton & Company, 1922, presents a brief and very clear account of the physiology of the hematopoietic system.

2. Hooper, C. W., and Whipple, G. H.: Am. J. Physiol. **42**:764, 1916-1917; ibid, J. Exper. Med. **17**:612, 1913.

3. Williamson, C. S.: Influence of Age and Sex on Hemoglobin, Arch. Int. Med. **18**:505 (Oct.) 1916.

extreme. The average drops from 21 gm. per hundred cubic centimeters of blood, at 2 weeks, to 13 gm. at 3 months of age. The variation among individuals of the same age group is still greater. In the chart, the middle line indicates the average of all the infants examined; the two other lines indicate the average of all those above and below the general average. From the sixth to the twelfth month the upper and



Grams of hemoglobin per hundred cubic centimeters in normal children.

lower limits of normal range from 10.8 to 14.2 gm. per hundred cubic centimeters. Or, to express this in the usual terminology, in the percentage of hemoglobin the normal variation ranges from 72 per cent. to 95 per cent.[4] Evidently, decision as to the presence and degree of

4. According to the standard used by us, 15 gm. per hundred cubic centimeters equals 100 per cent.

anemia must take into consideration, first, the variation dependent on age, and secondly, the individual variation within the age group.

With the exception of the infants that were only a few weeks of age, our cases were drawn from the "Feeding Ward" of the pediatric service of the New York Nursery and Child's Hospital. Few of the babies were vigorous and perfectly healthy; many were illnourished and underweight and a few suffered from slight ailments such as otitis, nasopharyngitis, mild impetigo, etc. All showed hemoglobin values above the lower limit of normal. As might be expected from their general condition, most of the hemoglobin percentages hovered about the lower rather than the upper limit of normal.

Hemoglobin determinations were made with Kuttner-Leitz hemoglobinometer.[5]

The method used for the determination of urobilin in the feces is that of Wilbur and Addis.[6] Certain modifications (the fact that we were working with infants' stools and used a different spectroscope) necessitate a description of the technic. Essentially, the method consists in the extraction of the feces and the addition of Ehrlich's reagent to the extract to produce the characteristic spectroscopic absorption bands of urobilin and urobilinogen. The quantity of the pigments is expressed by the number of dilutions necessary to cause the disappearance of the bands. The proportion of the two substances varies considerably and only the sum of their dilution values is of clinical significance; and hereafter the term urobilin without the mention of urobilinogen will refer to the combined value of the two. The daily variation in the excretion of urobilin is very great, and to minimize this variation repeated stool examinations are necessary. In all but a few of our cases the stools of our patients were examined for a period of six successive days. When spontaneous evacuation failed to occur, suppositories were used.[7]

Technic.—The soiled diapers were placed in metal cans immediately on their removal, to protect them from the light. All of the stool passed in the twenty-four hour period was used for the test. The feces were scraped from the diaper with a spatula and ground with tap water, just enough water being used to make a smooth suspension. When no urobilin at all or only a small amount was found, a more concentrated suspension was made on succeeding days. The stool suspensions varied

5. We are indebted to Dr. Soma Weiss for the standardization of the apparatus.

6. Wilbur, R. L., and Addis, Thomas: Urobilin: Its Clinical Significance, Arch. Int. Med. **13**:235-286 (Feb.) 1914.

7. In the original article of Wilbur and Addis a full discussion will be found of the relation of urobilinogen and urobilin to one another, the effect of constipation and diarrhea on urobilin excretion and the limitations of the test as a quantitative method.

from 25 c.c., the smallest amount that can be used, to 200 c.c. To 25 c.c. of this suspension were added 75 c.c. of acid alcohol (95 per cent. alcohol 1,600 c.c., concentrated hydrochloric acid 25 c.c., and water 800 c.c.), and the mixture was shaken thoroughly for thirty minutes. With this, an equal quantity (100 c.c.) of a saturated solution of zinc acetate in alcohol was mixed and shaken for a moment before filtering. To 20 c.c. of the filtrate, 2 c.c. of Ehrlich's reagent was added.[8] This was put aside in a dark place until the following day, when spectroscopic examination was made. The urobilinogen band is extremely sharp and lies between the red and the yellow. The urobilin band is not so distinct and lies between the yellow and the blue. Daylight or a Daylo lamp was used. The solution was diluted with 60 per cent. alcohol until first one and then the other band had disappeared.[9] The lowest dilution at which the band was still visible was considered the final reaction. The method of calculation was as follows: 25 c.c. of stool suspension plus 75 c.c. alcohol and 100 c.c. of zinc acetate in alcohol equals 200 c.c. Twenty cubic centimeters of this, or in other words, the extract of 2.5 c.c. of stool suspension was mixed with Ehrlich's reagent and used for the test. Thus the dilution required to cause the disappearance of the band gave the dilution value for 2.5 c.c. of stool suspension. If this figure is multiplied by the number of 2.5 c.c. quantities in the stool suspension, the number of dilutions is obtained that would be necessary if all the urobilin or urobilinogen were concentrated in the 2.5 c.c. of stool suspension. For instance, assume that a 100 c.c. stool suspension had been made. The urobilinogen band has disappeared after ten dilutions. There are forty 2.5 c.c. quantities in 100 c.c. Then forty times ten, or 400, equals the dilution value for urobilinogen. The urobilin band disappeared after five dilutions. Then forty times five, or 200, equals the urobilin dilution. The dilution value for total urobilin is 400 plus 200, or 600.

Table 2 summarizes the dilution values in the stools of sixteen infants under 1 year of age. Urobilin was found as early as the second week. Lucas [10] and his collaborators, who used the method of Wilbur and Addis, failed to find urobilin in the stools of infants under 10 weeks of age. Our technic differed in that more concentrated suspen-

8. Paradimethylamidobenzaldehyde 4 gm., concentrated hydrochloric acid 30 gm., water 30 gm.

9. Wilbur and Addis recommend a spectroscope with an attachment to control the light. They consider the end reaction to be that dilution at which the band is visible when the slit is narrowed and disappears when the slit is open. When we began our work, only a simple spectroscope without an adjustable slit was available. Recently we have used a finer instrument with an adjustable slit which is far more accurate and satisfactory.

10. Lucas, W. P., et al.: Blood Studies in the New-Born, Am. J. Dis. Child. **22**:525 (Dec.) 1921.

sions of feces were used, and this may account for the divergent results. In considering the wide variation in the amount of urobilin, the factors governing its excretion must be given due weight. Some and probably variable amounts may be reabsorbed; some also is destroyed in the intestines (Table 1). The amount also is influenced by the rate at which the feces pass through the intestinal canal; diarrhea increases and constipation diminishes the output. We do not know whether the kind of food and the nutritional condition of the infant are also factors. The variation is hardly more than to be expected, considering the wide variation in the urobilin excretion of normal adults, in whom Wilbur and Addis found values varying from 3,000 to 8,000.

TABLE 2.—*The Dilution Values in the Stools of Sixteen Infants Under 1 Year*

Case	Period of Observation, Days	Age	Weight, Pounds	Hemoglobin, Gm. per Hundred C.c.	Average Total Urobilin Values
1	6	3d to 10th day	6 $^{8}/_{16}$	20.5	0
2	7	5th to 15th day	5 $^{14}/_{16}$	18.1	15
3	8	3 weeks	6 $^{2}/_{16}$	18.1	10
4	8	4 weeks	9 $^{8}/_{16}$	14	53
5	6	6 weeks	6 $^{8}/_{16}$	13.1	109
6	7	9 weeks	7 $^{10}/_{16}$	11.5	30
7	7	3½ months	7	11.5	59
8	6	4 months	8 $^{8}/_{16}$	12.3	83
9	6	4½ months	11 $^{4}/_{16}$	12.6	119
10	6	5 months	10	13.1	40
11	7	6½ months	8	12.6	21
12	8	7 months	11 $^{10}/_{16}$	11.1	86
13	6	8 months	16	10.7	117
14	4	8 months	15 $^{14}/_{16}$	12.3	62
15	8	9 months	15	10.8	60
16	6	11 months	12 $^{4}/_{16}$	11.2	24

SUMMARY

1. The present conception that the status of the hemoglobin and formed elements of the blood is the result of a balance between blood destruction and regeneration, suggests the study of some of the anemias of infancy from that point of view.

2. The estimation of the degree of anemia must take into consideration the wide normal variations in the hemoglobin.

3. Urobilin is found in the stools of infants as early as the second week.

4. The urobilin of the stools of normal infants from 2 weeks to 1 year of age varies from fifteen to one hundred and fifty dilution units, according to the method of Wilbur and Addis.

MENINGEAL HEMORRHAGES IN THE NEW-BORN AND THEIR REMOTE CONSEQUENCES *

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PHILADELPHIA

From the onset of embryonic life up to the period of birth, the fetus is exposed to multiple damaging influences having a direct bearing on the growth of the central nervous system. Lesions of the latter may be numerous, and vary with regard to their localizations, extent and depth. They are apt to compromise the cerebral functions not only at the time the damage is done but especially during later development of the nervous system. If the infant survives, infirmities are seen not only in the sensorimotor sphere but also and more particularly in the mental faculties in which a definite defect is manifest. Of the many facts that are likely to lead to such consequences, only meningeal hemorrhages at birth will be discussed here.

During birth, hemorrhages may occur at different levels, either within the nervous tissue itself or close to the cranium. In the latter case, the blood may be located between the bone and its periosteum (cephalhematoma); between the periosteum and the dura, or beneath the dura.

In order to understand the mechanism of formation of hemorrhagic foci, a brief account of the anatomic arrangement of the membranes with their vascular supply is necessary.

The dura mater consists of two layers, an inner and an outer one. The outer, which is the periosteal membrane, sends septums into the cranial cavity accompanied by venous sinuses. These sinuses are the falx cerebri, which encloses the superior and inferior sagittal sinuses, also the straight sinus along the line of junction of the base of the falx with the tentorium; the tentorium cerebelli with the transverse and superior petrosal sinuses, and the falx cerebelli with the occipital sinus. The septums are reinforced in certain places by an aggregation of fibrous bands which enable the head to withstand the great strain in accouchement.

During a difficult labor, the frequent changes in the shape of the head and the excessive tension overstretch the septums, and tears follow. These tears may be complete or incomplete, unilateral or bilateral. When the tentorium cerebelli is involved, the tear is usually found below its junction with the falx cerebelli. When the falx cerebri is damaged, the

* Received for publication, Nov. 28, 1923.

* Read by invitation before the Obstetrical Society of Philadelphia, Oct. 12, 1923.

tear occurs at the level of its middle two thirds. Holland [1] found in a series of 167 cases tears in the tentorium in 48 per cent., and in all of the latter, subdural hemorrhages. The fine blood vessels and the large vein on the border of the small circumference of the tentorium are the sources of hemorrhages. The usual origin of hemorrhages is in the tributaries of Galen's vein received from the cerebellum and midbrain, and from the cerebellar veins entering the straight sinus. The experimental investigations of Holland prove this contention conclusively. These tributary veins are stretched between the fixed point of Galen's vein and the fixed cerebellum. During the excessvie tension in difficult labor the apex of the tentorium is drawn upward, and consequently the Galen's vein is twisted at its entrance into the sinus. An enormous distention of this vein and of its tributaries follows. On the other hand, the cerebellum is at that time pressed down into the posterior fossa by the undue pressure of the occipital lobes of the brain. Under such circumstances, the fine vein tributaries of Galen's vein, as well as the cerebellar veins entering the straight sinus, rupture.

Over the surface of the cerebral hemisphere, similar subdural hemorrhages may occur during difficult labor, and they are particularly intense in a foot presentation. They commonly occur between the layers of the falx cerebri, although less frequently than in cases involving the tentorium. Occasionally there may be a hemorrhage at the base of the brain. Rarely does the pia-arachnoid tear, but in such cases small hematomas occur.

Ventricular hemorrhages, although rare, may occur from extreme extension of the fine veins of the choroid plexuses.

The seat of hemorrhages is of importance. In the cases involving the tentorium, for example, even a small blood effusion beneath the tentorium would be of graver consequence than one on its surface however large it might be. Tears in the tentorium cerebelli are the most common occurrence. Those of the falx cerebri are next in frequency and are rather rare. In the majority of cases, they are associated with tears in the tentorium.

In considering the causes of meningeal hemorrhages, it is extremely important to bear in mind the immediate and the predisposing factors. Infections and intoxications in utero may be the direct cause, but the most frequent one is traumatism during the confinement, namely, extraction of the head last, forceps delivery from contracted pelvis or presentation of the face or of the forehead. As to breech presentation statistics show that tearing of the tentorium was found in about from 70 to 75 per cent. of dead fetuses thus delivered. Holland believes that in such cases the condition of the tentorium was due to the endeavor

1. Holland, E.: Report on the Causation of Foetal Death, London, Reports on Public Health, 1922.

to effect a rapid delivery after version; but if breech delivery is properly managed, there should not be sufficient intracranial tension to produce tearing of the tentorium. The same view can be applied to the cases with transverse presentation. Circulatory interference in the umbilical cord and congenital malformations of the central nervous system are also frequently the cause of intracranial hemorrhages.

The frequency of meningeal hemorrhages in the new-born may be seen from the statistics of Hedrén [2] of Stockholm, and Cruickshank.[3] The former examined 700 cadavers of infants and found intracranial hemorrhages in about 9.28 per cent. The bleeding was restricted to the meninges in nearly 84 per cent., and cerebral hemorrhage, accompanied by meningeal hemorrhage in others, brings the total of meningeal

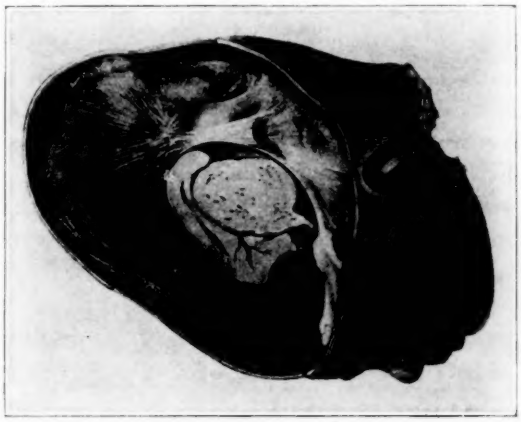

Fig. 1.—Incomplete tear of tentorium cerebelli on right side; the tear is across the fibers at the base of the anterior vertical band. The head shows extreme molding, after labor with generally contracted pelvis. Note elevation of apex of tentorium and change in direction of Galen's vein and straight sinus (Holland).

hemorrhages to 90.7 per cent. Delivery had been spontaneous in fifty of the sixty-five cases, and the conditions in both mother and child seemed to be normal in most of the cases. In the forty-two purely meningeal cases, the hemorrhage had been supratentorial in thirty-two, infratentorial in ten and of both types in six. An analysis of these cases leads to the conclusion that intracranial hemorrhages may occur with rapid and easy spontaneous delivery and they may occur without fracture of bone.

In Cruickshank's account of 200 cases, one finds the incidence of sixty-five cases which showed meningeal hemorrhages of a gross char-

2. Hedrén, G.: Intracranial Hemorrhage in the New-Born, Abstr. J. A. M. A. **70**:1988 (June 22) 1918.

3. Cruickshank, J. W.: Lancet. **1**:836 (April 28) 1923.

acter. In twenty-five cases there was meningeal hemorrhage associated with hemorrhage into the viscera.

CLINICAL MANIFESTATIONS

Meningeal hemorrhage is more frequently suspected than actually determined during life. Death may ensue in a few hours following the meningeal hemorrhage, but if the infant survives, a state of apparent collapse is observed, cyanosis, low temperature, convulsions on subsequent days, circulatory and respiratory disturbances, various palsies and contractures. When the infant further succeeds in overcoming the immediate effect of the bleeding, the above mentioned stormy symptoms gradually subside and the child enters into a chronic state of physical and mental inferiority with a crippled central nervous system. Diplegia, hemiplegia, spastic paraplegia, contractures, athetosic or choreiform movements, convulsive phenomena, amaurosis, mental deficiency or debility of various degrees—all form a symptom group which could be placed under one caption of infantile encephalopathies. Of course, this vast group presents various degrees in its extent and intensity. There are mild cases and cases in which the damage is profound. From the standpoint of intellectual development, the child may be an idiot or an imbecile, or may present only a slight degree of mentally arrested development. It all depends on the hemorrhage and on the facility with which the blood may be absorbed or otherwise removed.

The encephalopathies may be early or precociously diffuse, which will lead to idiocy; they may be late or delayed, circumscribed and frequently slight, which in adult life will be manifested in but slight disturbances of intelligence. The arrest of intellectual development will be especially pronounced and less amenable to improvement in those cases which, through hereditary factors, are inevitably predisposed to and prepared for disturbances or anomalies of cerebration.

A brief physiologic consideration is warranted. At birth, the cells of the central nervous system are fully developed. As to the nerve fibers, full growth is present only in those which control reflex movements, circulation, respiration and nutrition, in other words, the nervous mechanism of the spinal cord and medulla alone are functioning at that period of life. On the other hand, the fibers originating in the frontal, rolandic, occipital, parietal and temporal regions of the brain, as well as the projection and commissural fibers, become myelinated only some time after birth. It is evident, therefore, that early symptoms will be only those which are in relation to the physiologic function of the medulla and spinal cord, but manifestations depending on the function of various portions of the brain will be in evidence ulteriorly and for the above mentioned reasons will remain permanent. If we add to them

the compression of the convolutions caused by the blood, also the possibility of the breaking up of the cerebral tissue and infiltration of the latter with the blood, the physiologic damage is easily conceived.

A brief description of the several clinical varieties may be helpful for a full understanding of hemorrhagic possibilities.

CEREBRAL DIPLEGIA

Two important subvarieties should be considered. One is the classic Little's disease, in which there is a spastic paraplegia of the upper and lower extremities, and in which the spasticity is more pronounced than the paralysis but there are no convulsive phenomena and the intelligence

Fig. 2.—Complete tear of tentorium and extensive tearing of falx. In the tentorium there are two perforating tears on left side; one is a ragged tear starting below the base of the anterior vertical band and extending outward almost to the lateral border of tentorium. The other is a large perforation through the superior wall of the left lateral sinus at its termination in the torcular herophili (Holland).

is preserved. Improvement is a common occurrence. This form is fundamentally of agenesic order and due to a congenital insufficiency of the pyramidal tract. Premature birth is the original cause.

The second variety is due to destructive lesions of an inflammatory or traumatic origin, of a toxi-infectious or obstetric cause, namely, a difficult delivery producing tears in membranous blood vessels of the brain. Here the motor areas, as well as other portions of the cortex, are usually involved, spasticity and paralysis being produced, as well as serious convulsive phenomena and disturbance of intelligence. The condition is persistent, and is permanent. The clinical picture of the

last form of cerebral diplegia will vary according to the predominance of involvement of different areas. The association of intellectual phenomena with paralysis and spasticity of the limbs indicates a lesion in the frontal and rolandic areas. Here one or the other may predominate, but the presence of epileptiform manifestations is always an unfavorable condition for the intellectual development, and in all such cases the mental deficit is pronounced. Athetosic and choreic movements are also frequently observed in this variety of diplegia.

An interesting feature of the intellectual status in the first variety of diplegia deserves special mention. There is a striking discord between the appearance of the little patients and the real state of intelligence. At first glance, the difficult speech and the expression of the face with the mouth open may suggest a low mental state, but an actual test and close observation of their behavior and of their relation to the environment will reveal an integrity of intelligence.

The difference, consequently, between the two forms of diplegia is fundamental, and its second variety is far more serious than the first. Since it is due to obstetric traumas, the value of meningeal hemorrhages in difficult labor cannot be overestimated.

CEREBRAL HEMIPLEGIA

Should the hemorrhage be limited to one hemisphere, hemiplegia with all its characteristics will be the result. In almost all such cases, there is an intellectual deficit, more or less pronounced; all degrees between ordinary mental arrest and idiocy are observed. The inequality and irregularity in the intellectual deficit is due to the great variation in the extent and intensity of the lesions in one hemisphere. As to the hemiplegia itself, it differs from the same occurrence in an adult because, in addition to the paralysis there is considerable lack of development of the affected limbs: they are small not only as regards musculature but also bony tissue; there are permanent contractures with secondary deformities, hemiathetosic and hemichoreic movements; also, frequently, aphasia is absent in cases of right hemiplegia.

Frequently with, and in place of, complete or incomplete intellectual obliteration, other spheres of sensory psychic activity are developed, but close analysis will reveal that the latter are only of a purely reflex character, are automatic and lack in associative integration, and therefore lose all psychic value.

DOUBLE ATHETOSIS AND ATHETOSO-CHOREIC MOVEMENTS

As is shown in the foregoing, encephalopathies in infants may be manifested by a more or less marked deficit in the intellectual sphere, and accompanied by bilateral motor phenomena in the form of chorea

or athetosis. Again, various degrees of involvement may be present: there are cases with very slight disturbances in the psychic sphere, in which, on the contrary, the motor manifestations are most conspicuous. There are cases in which the two conditions are reversed. They are all observed in infants that were born by instrumental delivery, and consequently sustained traumas and suffered from meningeal hemorrhages during birth.

The three forms of encephalopathies described are the extreme and gross types. There are many intermediary forms which depend on the portion of the brain affected by the meningeal hemorrhage. Thus, any portion of the rolandic area may be affected: the centers of the leg or arm, face, lips or tongue may be individually compressed. There are cases with a minimum of diplegia; with pseudobulbar manifestations; with speech defects showing involvement of the speech centers, motor or sensory; with an exclusive mental defect indicating an involvement of the frontal lobes; with persistent and frequent epileptiform convulsions in which, particularly, the mental development suffers the most. Finally, there may be cases with unilateral or bilateral cerebellar manifestations, the so-called cerebellar hemiplegia or diplegia types, in which cerebellar manifestations alone are conspicuous.

CONCLUSIONS

The cause of meningeal hemorrhages is, principally, the tearing of the membranes due to their overstretching, which leads to rupture of the blood vessels. To produce a tear, there must be great cranial stress. Since the latter is frequently the result of protracted, difficult labor, with instrumental delivery, the obstetrician should bear in mind that the force used in the application of forceps should not be excessive, or should not be applied to the wrong diameter of the head, as, for example, the anteroposterior diameter. In the latter case, the vertical elongation of the head is, more than anything else, liable to cause overstretching and tearing of the meninges. Forceps are useful, and in many instances have been responsible for saving lives, but they may also be responsible for injuries in the fetus leading to consequences which have a direct bearing on the later physical and mental development of the child.

The preventive aspect lies in the consideration of all forces that are liable to lead to tearing of the meninges and the blood vessels. Wrong presentation and position of the fetus and other causes of difficult labor, such as prolapse of umbilical cord, the use of instruments or various manipulations in the delivery of the fetus, are all factors that cannot be overestimated in the production of cerebral hemorrhages and the tearing of the meninges.

Besides the preventive phase, let us consider briefly the therapeutic aspect of meningeal hemorrhage. With a certain degree of possible errors, supratentorial hemorrhages, generally speaking, present a somewhat different clinical picture from the infratentiorial type. In the former, the blood spreads over the hemispheres of the cerebrum; in the latter, over the hemispheres of the cerebellum but also into the medulla. In the former, the blood cannot go beyond the lower surface of the tentorium; in the latter, the blood reaches the subarachnoid space and may extend into the spinal canal.

For these reasons, in the supratentorial hemorrhage at birth one finds a bulging fontanel and a group of nervous phenomena, such as sleeplessness and great restlessness and convulsive seizures, with a continuation of the condition. In infratentorial hemorrhage, there is considerable depression, apathy, somnolence, early cyanosis, vasomotor and respiratory manifestations and rigidity of the neck muscles. In view of the anatomic differences, respiratory and other bulbar disturbances will not be observed in the cases of supratentorial hemorrhage.

Cyanosis is late in appearing and, when it does appear, is not pronounced in the supratentorial hemorrhages, but is early and very pronounced in the infratentorial cases; the anterior fontanel is at once bulging and early in appearance in the supratentorial, but slowly distending in the infratentorial cases.

For anatomic reasons, in infratentorial cases lumbar puncture may be of considerable benefit. Advocated first by Devraigne,[4] it was rapidly adopted by others, and favorable or very satisfactory results have been reported in the literature. Frequently, the withdrawal of spinal fluid needs to be repeated. In some cases, such as that of Lippman, one puncture may suffice. His patient presented convulsions, cyanosis, and frigidity. As the convulsions increased in intensity, Lippman [5] removed 25 c.c. of bloody spinal fluid. Complete recovery followed. In Green's [6] case, there were convulsions, cyanosis and apnea. Four punctures were made, 5 c.c. of bloody spinal fluid being removed each time, and all the symptoms disappeared. Brady [7] recently report very favorable results from lumbar punctures and removal of some spinal fluid. In the supratentorial cases lumbar puncture does not avail much, as the blood cannot reach the subarachnoid cavity easily. Surgical therapy is almost the only issue. Early craniotomy is directly indicated. Favorable results from the very nature of the condition can be expected only when an operation is performed within a few days after birth. After

4. Devraigne: Thèse de Paris de Dutreix, 1905.
5. Lippman, U. J.: New York M. J. **103**:263 (Feb. 5) 1916.
6. Green, R. M.: Bost. M. & S. J. **174**:947 (June 29) 1916.
7. Brady, J. U.: Lumbar Puncture in Meningeal Hemorrhage of the New-Born, J. A. M. A. **71**:347 (Aug. 3) 1918.

the clot has already produced damage to the cortical tissue, no relief can be expected. Cushing,[8] who obtained four complete recoveries in nine cases, is of the opinion that no hesitation should exist in operating on such young infants, in view of the fact that the new-born can withstand cranial operations better than any other operation and that much less traumatism is created by an operation than by the passage of the head through the pelvis during birth. With proper hemostasis and proper preservation of the body temperature during the operation, the possibility of surgical success, Cushing claims, is secured. In his fatal cases, he found extensive extravasation over entire hemispheres, and the patients were in a dying condition. Not too much, he counsels, should be attempted at one sitting, and a secondary intervention is advisable.

Henschen[9] advised aspiration of the cranial subdural space in supratentorial cases, followed by an incision through the coronal suture. Brady suggests in supratentorial cases, first a lumbar puncture, and immediately afterward incision below the parietal suture. It seems logical that in all cases indicating increased intracranial pressure at birth, lumbar puncture should be resorted to at once, before a definite localizing diagnosis is made, since in the infratentorial group it is of definite therapeutic value, and in the supratentorial group the diagnosis may be promptly established.

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8. Cushing, Harvey: Surgery of the Head, Philadelphia, W. B. Saunders Company, 1908.
9. Henschen: Verhandl. d. Deutsch. Gesellsch. f. Chir. **41**:271, 1912.

STUDIES ON THE ACIDITY (HYDROGEN ION CONCENTRATION) OF INFANTS' STOOLS*

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The number of investigations of the exact acidity, that is, the hydrogen ion concentration, of infants' stools reported in the literature are comparatively few. When the possible importance of the relation of the acidity of the stools to the general condition of the infant, the rate of growth, the presence of fermentative diarrhea, parenteral infections and many other conditions are considered, it is rather surprising that so few determinations have been reported. The only results which we have been able to find have been recorded in the German literature.

The earliest reported figures on the p_H of infants' stools are those recorded by Eitel[1] in 1917. He found that stools from breast fed infants usually had an acidity of p_H from 4.6 to 5.6, although many values were obtained outside these limits. Stools from infants fed on cows' milk dilutions in the majority of cases gave values which varied from p_H 7.8 to 8.2. He found that buttermilk feeding also gave alkaline values, the average being p_H 8.0. Malt soup, on the other hand, gave acid values usually between p_H 5.4 and 6.0. Freudenberg and Heller,[2] in 1921, found that the p_H of stools from normal breast fed infants generally varied from 4.8 to 5.6. Similar values were obtained by Hess and Scheer[3] in a study on the acidity of infants' stools in relation to dysentery. These authors found that stools from infants fed on buttermilk usually had an acidity from p_H 7.6 to 8.2 and stools from infants on half milk and half water an acidity from p_H 7.2 to 8.6. Whether any carbohydrate was added to the last two types of feeding was not stated. All these authors used the electrometric method for the determination of the p_H of the stools.

Meaning of the Term p_H.—A great deal of work has been done by investigators who have taken a measured portion of an infant's stool and titrated this with an alkali to the point of neutrality. This however determines not only the amount of free acid present, but also

* Received for publication, Jan. 21, 1924.

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1. Eitel, H.: Ztschr. f. Kinderh. **16**:13, 1917.
2. Freudenberg, E., and Heller, O.: Jahrb. f. Kinderh. **95**:314, 1921.
3. Hess, R., and Scheer, K.: Arch. f. Kinderh. **69**:370 (May) 1921.

a portion of the acid which has already combined with certain bases. At first glance it would appear that if the acid were combined with a base it would be neutral and thus not enter into this titration, but it must be remembered that all salts are not neutral in reaction. One example of this is acid sodium phosphate. It is thus obvious that these titrations have not the same significance or value as the determination of the exact degree of acidity present in the stool.

The question arises as to what constitutes the degree of acidity of a solution. The degree of acidity of a solution depends on one thing; that is, the number of free hydrogen ions present. When a substance such as ordinary salt is placed in a solution it is present in two forms, first, as molecular or undissociated sodium chlorid, which is chemically inert, and secondly, as dissociated (ionized) or chemically active sodium and chlorin ions. Similarly, acids in solution are present in two forms, the molecular or inactive and the dissociated or active forms. All acids, however, on dissociation must give free hydrogen ions (H^+) regardless of the type of acid. Some acids are stronger than others, which simply means that they are more completely dissociated or ionized than the others. Hydrochloric acid is an example of a strong acid, as it is practically entirely dissociated into its hydrogen and chlorin ions. Acetic acid is a weak acid because it is only slightly dissociated (about 2 per cent.); by far the greater part being in the molecular or inactive form.

If the degree of acidity of a solution depends on the number of free hydrogen ions, then the acidity may be measured by determination of the amount of hydrogen ions present in the solution. This is exactly what is done when the acidity is measured. The concentration of the hydrogen ions, and consequently the degree of acidity, is expressed in terms of a fraction of a gram of hydrogen ions per liter of solution. Thus a solution may have an acidity of one tenth of a gram of hydrogen ions per liter or one ten millionth of a gram, or any other amount. It is obvious, however, that this is a very cumbersome method of expressing the acidity of a solution, so the logarithmic notation, first suggested by Sörensen, is used. Thus, a solution containing one tenth of a gram of hydrogen ions per liter is expressed as 10^{-1}, or $\frac{1}{10^1}$; one one-hundredth of a gram as 10^{-2}, or $\frac{1}{10^2}$; one one-thousandth of a gram as 10^{-3}, or $\frac{1}{10^3}$; and so on. Even this, however, is a little cumbersome, so the figures 1, 2, 3, etc., are used in place of 10^{-1}, 10^{-2}, 10^{-3}, etc., preceded by the symbol p_H. Consequently p_H 1, 2 or 3, as the case may be, simply mean a definite amount by weight of hydrogen ions per liter of solution.

A solution with a p_H 1 (or one tenth of a gram of hydrogen ions per liter) is strongly acid; a solution with an acidity of p_H 7 (or one ten-millionth of a gram of hydrogen ions per liter) is neutral and if the

concentration is less than one ten-millionth as expressed by p_H 8, 9, 10, etc., it is alkaline. It is beyond the scope of this paper to enter into a discussion of the means by which the amount of hydrogen ions are directly determined, other than to state that this is accomplished by expensive electrometric apparatus.

METHODS FOR THE DETERMINATION OF THE p_H OF SOLUTIONS

As has been stated, the only means of directly measuring the p_H of a solution is by electrometric apparatus. It has been found, however, by careful electrometric measurements that with definite concentrations certain solutions such as monobasic and dibasic phosphates, or sodium citrate and hydrochloric acid, mixed in definite proportions, result in solutions which have a definite and constant p_H. Consequently, it is not difficult to make up solutions with a known hydrogen ion concentration. Having made up these solutions it is easy to develop in each of them a definite color which is constant for each p_H. This is done by the addition of substances called indicators. Each indicator develops its variation in color over a limited range of hydrogen ion concentration. For example, if a few drops of phenolsulphonephthalein are added to solutions whose p_H vary from 6.6 to 8.4 the color ranges from a light yellow to a deep red. If the solution is more acid than p_H 6.6, or more alkaline than p_H 8.4, other indicators must be used. When a set of standards has been made and suitable indicators added, the acidity of an unknown solution may be determined by the addition of an equal amount of the indicator used with the standard, and subsequent comparison of the color developed with that present in the standard solution. This constitutes what is known as the colorimetric method. It has the advantage over the electrometric method in that it does not require an expensive apparatus and is not so time consuming. At the same time it gives results which are comparatively accurate.

The value of the colorimetric method for the determination of the p_H of stools is seriously impaired because of the difficulty in obtaining a clear and colorless fecal extract. It is obvious that the presence of turbidity, or color, interferes with the accuracy of the method. Also the presence of proteins interferes with the action of some indicators. Howe and Hawk [4] found it practically impossible by filtration through paper or by centrifugation to obtain an extract which was not turbid or colored. Nelson and Williams [5] attempted to overcome this difficulty by centrifuging and filtering the stool extract through two thicknesses

4. Howe, P. E., and Hawk, P. B.: J. Biol. Chem. **11**:129, 1912.
5. Nelson, C. F., and Williams, J. L.: J. Biol. Chem. **28**:231 (Dec.) 1916.

of filter paper. Rettger and Cheplin [6] also used the same procedure. The values obtained, however, by this method on normal adult stools were much more acid than those recorded by Howe and Hawk, and later by Robinson,[7] all of whom used the electrometric method. Most investigators, on account of the above mentioned difficulties, have used the electrometric method for the determination of the p_H of stools.

For the present investigation of the p_H of infants' stools, we have utilized a simple and well known procedure by means of which colorimetric determinations have been made with rapidity and accuracy. In 1915, Levy, Rowntree and Marriott [8] suggested the use of collodion sacs for the determination of the p_H of blood. The blood was dropped into these sacs and dialyzed for five minutes. The dialysate was found to be free from proteins and coloring matter but contained blood salts, and was well adapted for use with indicators. In 1920, Kramer and Greene [9] utilized collodion sacs for the colorimetric determination of the p_H of milk and obtained results that were found to be quite accurate when checked by electrometric determinations. It is obvious that the same principle can be used for the determination of the acidity of stools, and in the following paragraphs are given the details of the procedure devised by one of us (F.F.T.) for the present investigation.

PROCEDURE FOR DETERMINATION OF p_H OF STOOLS

Standard solutions from p_H 5 to p_H 8.3 are obtained by the use of anhydrous dibasic sodium phosphate and acid potassium phosphate. Tenth normal solutions of each are used. The amounts used (Table 1) were obtained from a curve prepared by Sörensen.[10] Tenth molar sodium citrate and tenth normal hydrochloric acid are used to obtain solutions from p_H 3 to p_H 4.8. The tenth molar sodium citrate is made by dissolving 21.008 gm. citric acid in 200 c.c. of normal sodium hydroxid and adding water to 1,000 c.c. The amounts used (Table 2) were also obtained from a curve prepared by Sörensen. The indicators used are as follows: Methyl orange from p_H 3 to 4.4; methyl red from p_H 4.6 to 5.6; dibromorthocresolsulphonephthalein from p_H 5.8 to 6.4; phenolsulphonephthalein from p_H 6.6 to 7.6 and orthocresolsulphonophthalein from p_H 7.8 to 8.3. The standards may be used for over a month without the colors changing, with the exception of the methyl

6. Rettger, L. F., and Cheplin, H. A.: A Treatise on the Transformation of the Intestinal Flora with Special Reference to the Implantation of *Bacillus Acidophilus*, New Haven, Yale University Press, 1921.

7. Robinson, C. S.: J. Biol. Chem. **52**:445 (June) 1922.

8. Levy, R. L.; Rowntree, L. G., and Marriott, W. McK.: A Simple Method for Determining the Hydrogen-Ion Concentration of the Blood, Arch. Int. Med. **16**:389 (Sept.) 1915.

9. Kramer, B., and Greene, C. H.: Proc. Soc. Biol. Chem. (Dec.) 1920, reported in J. Biol. Chem. **46**: XXXVIII, 1921.

10. Neuberg, C.: Der Harn, Berlin, Julius Springer, **2**:1574, 1911.

red, which generally fades slightly within a week's time. Alpha-naphthylaminazosulfanilic acid was tried in place of methyl red but it was also found to fade, with the added disadvantage that the color changes were not so marked.

TABLE 1.—*Amounts of Tenth Normal Dibasic Sodium Phosphate and Tenth Normal Monobasic Potassium Phosphate Necessary to Obtain Standard Solutions from P_H 5.0 to P_H 8.3.*

p_H	C.c. Tenth Normal $Na_2HPO_4 + 2H_2O$	C.c. Tenth Normal KH_2PO_4	p_H	C.c. Tenth Normal $Na_2HPO_4 + 2H_2O$	C.c. Tenth Normal KH_2PO_4
5.0	0.04	3.96	6.8	2.00	2.00
5.2	0.08	3.92	7.0	2.48	1.52
5.4	0.14	3.86	7.2	2.92	1.08
5.6	0.20	3.80	7.4	3.28	0.72
5.8	0.32	3.68	7.6	3.54	0.46
6.0	0.48	3.52	7.8	3.76	0.24
6.2	0.74	3.26	8.0	3.90	0.10
6.4	1.08	2.92	8.3	4.00	0.00
6.6	1.48	2.52			

TABLE 2.—*Amounts of Tenth Molar Sodium Citrate and Tenth Normal Hydrochloric Acid Necessary to Obtain Standard Solutions from P_H 3.0 to P_H 4.8*

p_H	C.c. Tenth Normal Sodium Citrate	C.c. Tenth Normal HCl	p_H	C.c. Tenth Normal Sodium Citrate	C.c. Tenth Normal HCl
3.0	1.60	2.40	4.0	2.24	1.76
3.2	1.70	2.30	4.2	2.44	1.56
3.4	1.80	2.20	4.4	2.72	1.28
3.6	1.94	2.06	4.6	3.04	0.96
3.8	2.08	1.92	4.8	3.48	0.52

Collodion sacs are prepared practically according to the directions outlined by Levy, Rowntree and Marriott.[8] Half an ounce (14 gm.) of collodion is dissolved in 250 c.c. of a mixture of equal quantities of ether and ethyl alcohol. It dissolves, with occasional shakings, in forty-eight hours. A small test tube (1.3 cm. inside measurement, by 12 cm.) is filled with this mixture, inverted and the contents allowed to run out slowly. Care must be taken to rotate the tube in order to secure a uniform thickness throughout. The tube is clamped in the inverted position and allowed to stand from ten to fifteen minutes. It is then filled a few times with cold water. A knife blade is run around the upper rim so as to loosen the sac from the rim of the test tube, and then a fine glass rod is gently inserted between the sac and the wall of the test tube. The tube should be kept full of water and by gentle manipulation with the glass rod, the sac can be separated from the tube.

It should then be preserved by complete immersion in water. The sacs can be used again and again until they are torn or otherwise destroyed.

The stools were obtained from the infant by inserting a glass rod in the rectum and when being passed were collected directly in a small evaporating dish. They were then put in the ice box. It was found that their p_H did not change during the next twenty-four hours. However, the determinations were generally made the day the specimens were obtained. A small amount of freshly distilled and boiled water (from 15 to 20 c c.) is added to the fecal material in each evaporating dish and thoroughly mixed by means of a glass rod. The minimum amount of stool necessary is a piece about the size of a large pea. This emulsion is poured into the collodion sac which in turn is inserted in a test tube (1.7 cm. inside measurement by 15 cm.) containing 10 c.c. of the boiled distilled water. Dialysis is allowed to proceed for from twenty to thirty minutes, the sac being then removed leaving 10 c.c. of a clear and colorless fluid which has the same p_H as that of the stool. Four cubic centimeters of the dialysate are poured into a test tube of the same size as that of the tubes containing the standard solutions, and a few drops of the indicator is added. If the proper indicator is not selected at the first trial there is sufficient dialysate left for repetition. The color developed is compared with that in the standard tubes.

The method as outlined above has the advantage of requiring comparatively little time. It also gives results which for clinical purposes compare favorably with those obtained by the electrometric method (Table 3).

TABLE 3.—*Comparison of the Results Obtained by the Colorimetric Method and the Electrometric Method for the Determination of the p_H of Stools* *

Standard Solutions	Colorimetric Method	Electrometric Method	Stools No.	Colorimetric Method	Electrometric Method
p_H 3.0	—	3.06	1	5.8	5.76
p_H 4.6	—	4.64	2	6.2	6.16
p_H 5.6	—	5.66	3	6.8	6.78
p_H 6.8	—	6.82	4	7.6	7.50
			5	8.0	8.00

* The authors are indebted to P. J. Moloney, of the Connaught Laboratories, for the electrometric determinations.

RESULTS

During last summer, over 1,300 determinations were made of the p_H of infants' stools. The object of the investigation was not to study the effect on the p_H of the stools of carefully prepared variations in

the diet, but rather to determine the acidity as a routine procedure over a considerable period of time. Although it was quite evident at the beginning of this work that a number of the results would be of little use, still it was hoped that valuable information might be obtained where possibly least expected. In our opinion the results obtained have justified the procedure.

With the exception of a few stools from newly born breast fed infants, all the specimens were obtained from artificially fed babies. They varied in consistency and appearance from that of loose green

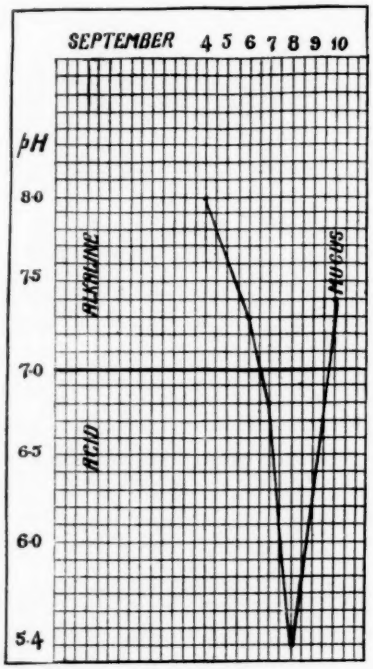

Chart 1 (Case J. F.).—An alkaline reaction produced by the presence of mucus. September 6, the stool was brown, pasty; September 7, yellow, pasty; September 8, yellow, curdy; and September 10, yellow, fluid with mucus.

diarrheal stools to that of hard brown constipated stools. It was soon found that the presence of mucus produced an alkaline reaction. As a result of this, many diarrheal stools which contained mucus gave an alkaline reaction when it was quite evident that the underlying condition was an increased acidity of the intestinal contents (Chart 1). This is probably the explanation of some of the conflicting statements made by older writers that diarrheal stools, under fermentative conditions, may have an alkaline reaction. It was also found that the brown, formed, constipated stool was not nearly so alkaline as the pasty stool,

and in other cases it was observed that reactions as alkaline as p_H 8.3 were obtained with stools of a fluid to semifluid consistency. This simply demonstrates that the firmness of a stool may give little indication of the degree of acidity present. Most of the stools with a reaction more acid than p_H 6.6, with the exception of diarrheal watery stools, were of a curdy consistency and had an acid odor. Values were obtained from the stools of artificially fed babies, which varied from

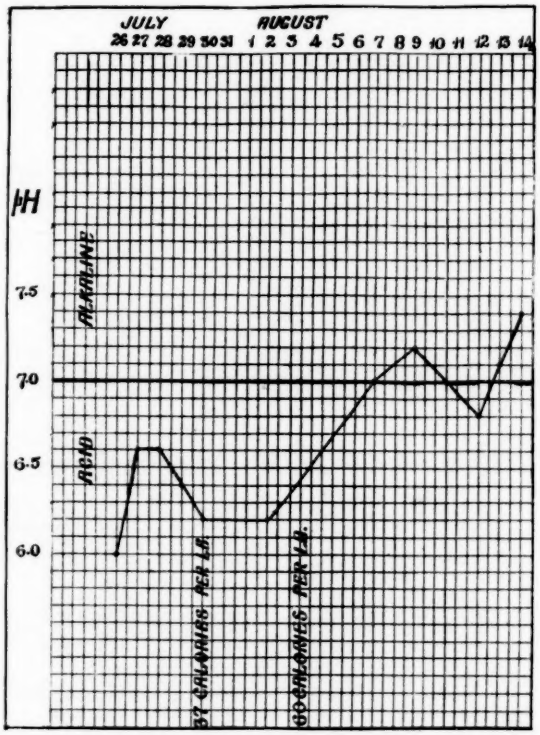

Chart 2 (Case G. L.).—Aged 2 months, weight 8 pounds (3,638 gm.). The reaction of the stools from acid to alkaline may be changed by the addition of carbohydrate to protein milk. The diet on July 27 was 30 ounces (850 gm.) protein milk (powdered preparation) two-thirds strength; July 30, ⅔ ounce (19 gm.) of casic was added, and on August 4, 1 ounce (28 gm.) of corn syrup was added.

p_H 4.6 to slightly more alkaline than p_H 8.3. As stools were rarely encountered with an alkalinity of more than p_H 8.3 the standards were not extended beyond this value.

Determinations to the extent of twelve in number were made of the acidity of stools from breast fed infants. As practically no infants were admitted to the hospital during last summer who received breast milk exclusively, specimens were obtained from the Burnside Clinic of

the new-born. All the infants were under 2 weeks of age. The p_H was found to be singularly constant. It varied only from p_H 4.7 to 5.1 in the twelve specimens examined.

In a general way, it was found that the degree of acidity of the stools was largely dependent on the type of food used. The stools from the normal breast fed infants mentioned above had an acidity of about p_H 5.0. Infants fed on buttersoup [11] generally had stools with a p_H of about from 5.8 to 6.2, while the stools from infants fed on protein milk, cows' milk dilutions with added carbohydrate, or whole

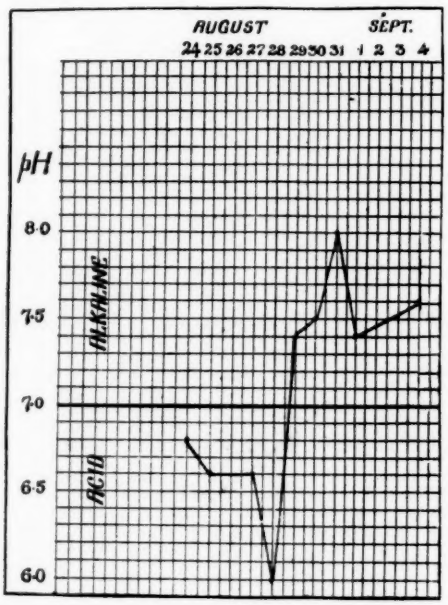

Chart 3 (Case R. N.).—Aged 12 months. Weight 17 pounds (7,711 gm.). The reaction of the stools from acid to alkaline may be changed by the addition of carbohydrate to soured milk. Until the afternoon of August 27, this infant was on 40 ounces (1,134 gm.) of 2 per cent. soured milk and 1 ounce (28 gm.) of dextri maltose. The stools, which were yellowish green in color, contained a lot of fat curds. They could not be characterized as good stools. On the afternoon of August 27, the feeding was changed to 25 ounces (718 gm.) of 4 per cent. soured milk, and 3½ ounces (100 gm.) of granulated sugar. By August 30, the stools were of a yellow-gray pasty appearance. It is to be noted that the total amount of fat given was practically unchanged.

soured milk with added carbohydrates were generally more alkaline than p_H 7.0. It has usually been considered that protein milk with its low sugar content would produce an alkaline stool, while a feeding with

11. Brown, A.; Courtney, A. M., and MacLachlan, I. F.: A Clinical and Chemical Study of Butter Soup Feeding in Infants, Am. J. Dis. Child. **24**:368 (Nov.) 1922.

a high carbohydrate content would produce an acid stool. In this connection some very surprising results were obtained. In certain instances it was found that infants fed on protein milk or soured milk had acid stools which remained acid until carbohydrates were added to the diet (Charts 2 and 3). Also it was found that the most alkaline stools were obtained from infants fed on whole soured milk with a total carbohydrate content as high as 20 per cent. No consistent difference was found in the acidity whether the carbohydrate was added in the

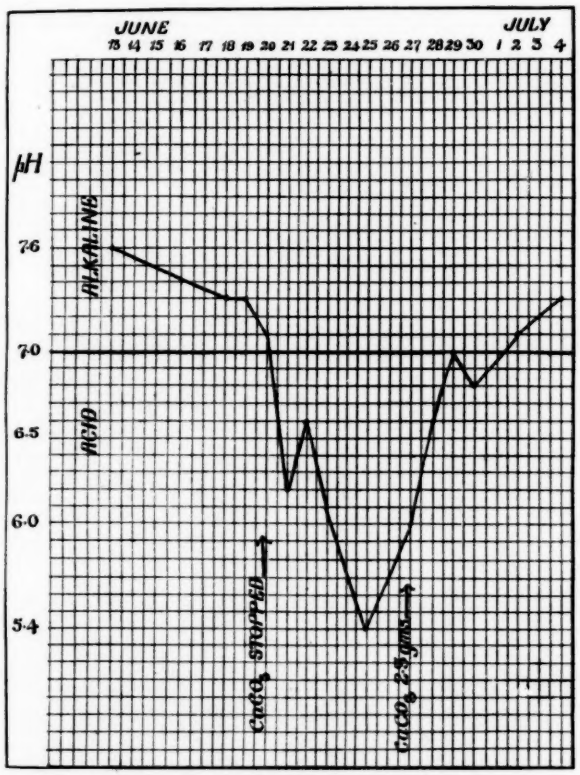

Chart 4 (Case J. D.).—The effect produced on the acidity of the stools by the addition of calcium carbonate to a diet containing a small amount of calcium salts. This infant was fed 14 ounces (396 gm.), of buttersoup, 7 ounces (198 gm.) of whole milk and 2.3 gm. calcium carbonate. The calcium carbonate was omitted and then replaced with the above result.

form of corn syrup, dextri maltose or cane sugar. The values obtained with one baby (W.B.) serve as an example. This infant was studied over a period of three and a half months. The diet consisted of whole soured milk with added carbohydrate up to a total content of 12 per cent. for the first two and a half months, then to just under 20 per cent. for the following month. During this period the acidity of the

stools was determined sixty-three times. Of these sixty-three determinations, only four were more acid than p_H 7.6. The values generally ranged from p_H 7.6 to 8.3. The stools were large, brownish, gray and soapy and when the inner part was exposed had a greasy appearance.

The effect of the addition of calcium carbonate to the food was determined in a few instances. It was found in certain cases that the addition of fairly large quantities (2.3 gm. per day) of the salt to buttersoup feeding made the stool more alkaline (Chart 4). On the

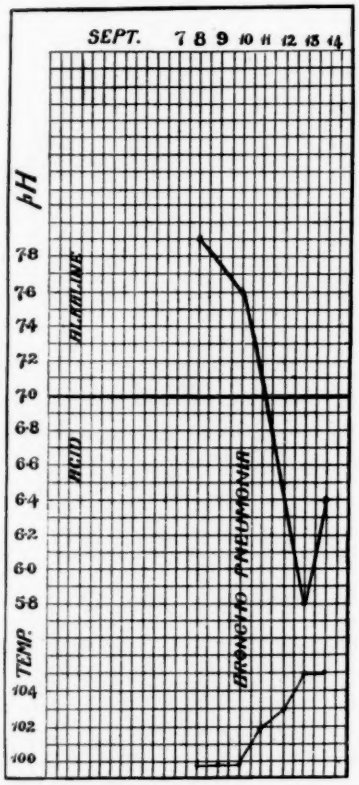

Chart 5 (Case R. S.).—The change produced in the acidity of the stool by the presence of a parenteral infection.

other hand, in diarrheal conditions it produced practically no change. Although not sufficient cases were studied to draw authoritative conclusions, still, it appears that while the addition of calcium carbonate to the food in normal cases makes the stool more alkaline, in diarrheal conditions it has little effect.

Observations were made on the effect of parenteral infections in a large number of cases. In the majority of instances the acidity of the stools increased and the smooth and pasty consistency changed to a

slightly loose and curdy consistency (Chart 5). In other infants the presence of parenteral infections seemed to have no effect either on the p_H of the stools or on their consistency (Chart 6). In one infant rather unusual results were obtained. This baby (Chart 7) developed pyelitis and the stool, observed daily, showed the following changes: August 30, brown semi-formed; August 31, loose, grayish curdy; September 1, brown fluid with mucus; September 2, very watery with a few green curds and mucus. Yet in this case the p_H never became

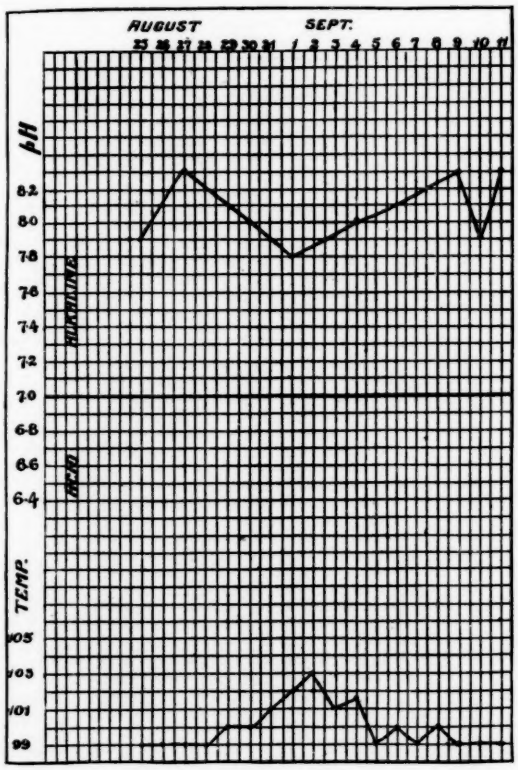

Chart 6 (Case W. B.).—The acidity of the stool is practically unaltered in some cases in the presence of a parenteral infection. The consistency of the stools in this case did not change during the infection.

more acid than 7.1. It is probable that the early production of mucus more than neutralized the effects of any acids present. It is of interest to note that shortly after this, the infant showed evidences of a prolapse of the rectum, which condition may have been a factor in the early production of mucus. From the foregoing observations it appears that parenteral infections generally cause an increased acidity of the stool, although there are many exceptions to this rule.

The question arises whether the acidity of the stool has any connection with the rate of growth of the infant. The answer may be both in the negative and the affirmative. It is well known that infants gain well on foods which normally produce acid stools, such as breast milk, buttersoup and malt soup. It is also obvious that they may gain just as well on foods which normally produce alkaline stools, such as whole milk dilutions or whole soured milk, with added carbohydrates. It was found however, that if the acidity was greater than that which is normally found with the particular type of food given, the infant did not do well.

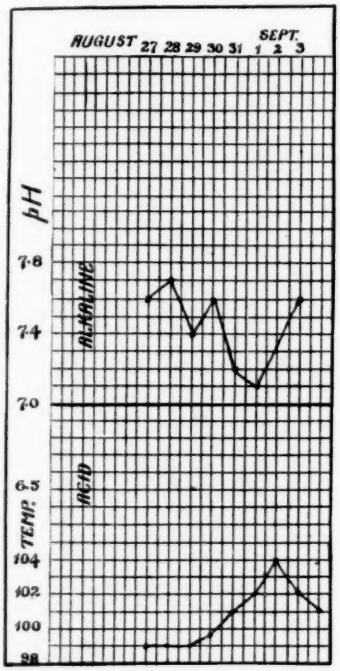

Chart 7 (Case K. S.).—This infant, in the presence of a parenteral infection, developed loose watery stools with a few green curds and mucus. The stools did not show the preliminary acid reaction before the presence of mucus was noted.

Some further observations made during the course of these investigations are of interest. When the food was changed from buttersoup to either whole milk dilutions or whole soured milk, with added carbohydrates, the p_H of the stool changed with surprising rapidity. If the change in the food was made at 2 p. m., the stools obtained the next day at 9 a. m. were of a different consistency and of a much more alkaline reaction (Chart 8). Another point of interest observed was that in occasional cases when an infant was given a food which would

normally produce an alkaline stool, the reaction would be acid for some days, then for no apparent reason the stool would suddenly change in consistency and become alkaline (Chart 9). A third observation of interest was that in certain infants the acidity of the stools showed wide daily variations. No apparent cause for this was found (Chart 10).

CONCLUSIONS

It is now widely recognized that of the three main organic constituents of infant's food, that is, the fats, the carbohydrates and the

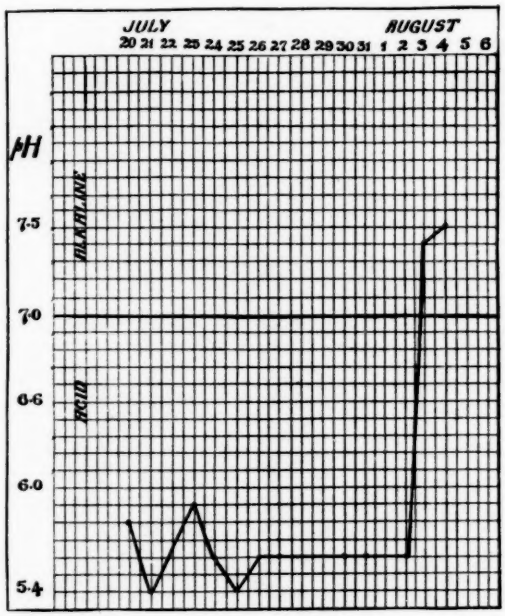

Chart 8 (Case B. J.).—The rapid change in the acidity of the stools with a change in the food. On August 2, the food was changed from buttersoup to a whole cows' milk dilution with added carbohydrate.

proteins, it is chiefly the carbohydrates that are concerned with the production of acid. This production of acid is the result of the fermentative action of microorganisms which break down the carbohydrates into lactic, acetic, formic, butyric and succinic acids. Lactic acid is the acid that is produced in the largest quantities, although occasionally a considerable amount of acetic acid may be present. Only traces of the other acids are found.[12]

12. Tobler, L., and Bessau, G.: Allgemeine Pathologische Physiologie der Ernahrung und des Stoffwechsels im Kindersalter, Wiesbaden, J. F. Bergmann, 1914, p. 183.

Fats are normally broken down by some of the intestinal secretions into the higher fatty acids and glycerine. These higher fatty acids, however, are nonirritating, or at most only slightly so. It has not been conclusively demonstrated that bacteria can split fat or break down the nonirritating higher fatty acids into the irritating lower fatty acids.[13] At the same time the presence of fat and the higher fatty acids may have a stimulating effect on the growth of bacteria and thus indirectly increase the acidity.[13]

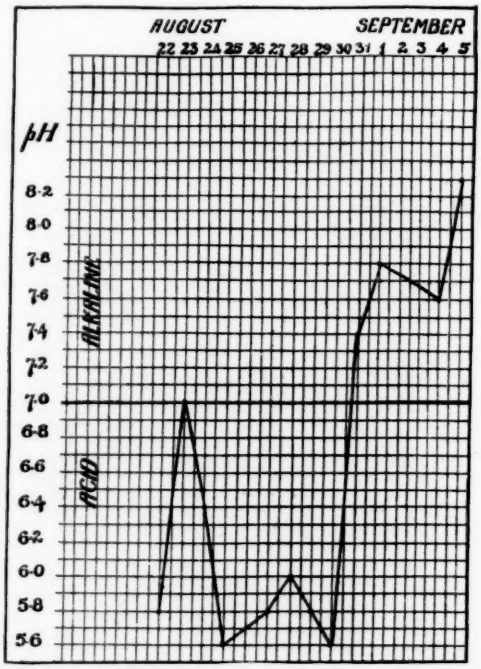

Chart 9 (Case M. K.).—On August 22, the food in this case was changed from 20 ounces (567 gm.) of 2 per cent. soured milk, and ½ ounce (14 gm.) of corn syrup to 20 ounces (567 gm.) of 4 per cent. soured milk, and 3 ounces (85 gm.) of dextri maltose. A marked change in the acidity of the stool did not occur until August 30, eight days later. No reason was found for this delayed action.

The proteins are affected by many microorganisms and various products are found such as indol, skatol, certain amin bases, and ammonia. From our standpoint we are chiefly interested in the ammonia production on account of its alkaline reaction. Certain acids may be formed in small quantities but their effect is greatly overbalanced by that of the ammonia produced. It is thus evident that bacterial action on proteins, with the resultant liberation of ammonia, tends to produce an alkaline reaction.

13. Schiff, E., and Kochmann, R.: Jahrb. f. Kinderh. **99**:181 (Sept.) 1922.

From the foregoing statements it would appear that the reaction of a stool depends largely on the ratio of the carbohydrates to the protein in the food. Although this is true, nevertheless there are a number of other factors which greatly influence the reaction of the feces. These will be discussed briefly.

It is known that, normally, bacterial growth in the intestinal canal is almost entirely limited to the lower part of the ileum and the large intestine. As the production of acid from carbohydrates is accomplished by the action of microorganisms it is obvious that this production

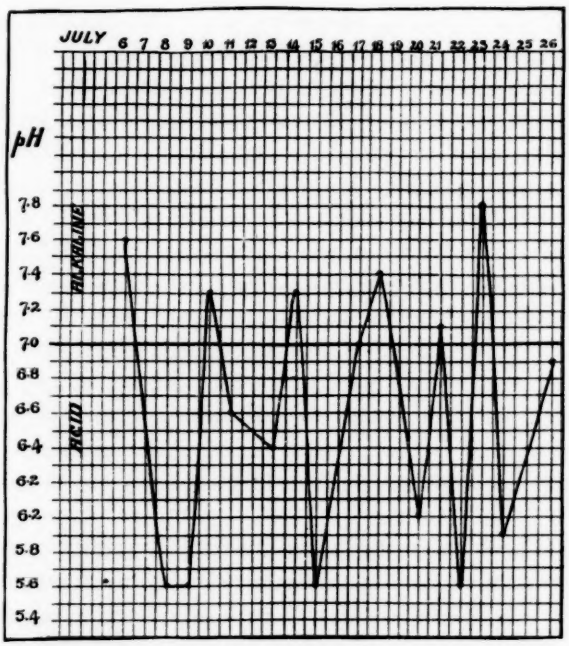

Chart 10 (Case H. S.).—The wide daily variations in the acidity of the stool which was encountered only occasionally. No apparent cause was found for these variations.

of acid must occur in the lower ileum and the large intestine, the so-called zone of fermentation. If normally no fermentation occurs in the upper part of the small intestine, and sugars can be absorbed by this part of the intestine, it is clear that one of the important factors in the production of acid is not the amount of sugar in the food but the amount of sugar which reaches and remains in the zone of fermentation. This point has been strongly emphasized by Bessau.[14] Freudenberg and Heller [15] have demonstrated most clearly that the rate

14. Bessau, G.: Jarhb. f. Kinderh. **92**:14, 1920.
15. Freudenberg, E., and Heller, O.: Jahrb. f. Kinderh. **96**:49, 1921.

of absorption of a sugar has a definite effect on the acidity of the stool. Utilizing the fact that caramel is poorly absorbed by the intestinal mucosa,[16] Freudenberg and Heller fed an infant a whole cows' milk dilution containing 80 gm. of caramelized cane sugar. The caramelization was accomplished by heating the cane sugar in an open pan until it was of a dark brown color. The p_H of the stool was found to vary from 4.7 to 5.0. The cane sugar was then added without being caramelized and the stool promptly became alkaline with a p_H of 6.7 to 7.4. It is obvious, therefore, that the rate of absorption of the carbohydrate by the intestine is an important factor in the production of acid.

As the production of acid from carbohydrates is the result of bacterial action, different bacteria may produce different degrees of acidity. That this is so has been clearly demonstrated. Michaelis and Marcora,[17] Clark,[18] Scheer [19] and others have found that the colon bacillus will not produce an acidity greater than p_H 5.0 and that when the acidity is greater than this (p_H 4.6) the colon bacillus is killed. *Streptococcus lacticus* produces an acidity of p_H 4.2 to 4.6 while the *Bacillus bifidus* produces an acidity as great as p_H 3.7.[20] It is well known that in alkaline stools the bacterial flora is largely gram negative while in acid stools the flora is preponderantly gram positive (*B. bifidus, B. lacticus, B. acidophilus,* etc.). The question at once arises, is the acidity of the stools the result of an infection and subsequent growth of an acid producing organism, or is the presence of these organisms secondary to other factors? It would appear most reasonable to assume that acid stools are the result of an infection, and the resultant preponderant growth of the acid producing gram positive organisms. This question has been investigated at some length by many bacteriologic workers. Their results will not be discussed here. However, a series of experiments from the chemical standpoint have been reported by Scheer [20] which are most interesting. He inoculated various milk media with stools from infants fed on breast milk and also from infants fed on protein milk. In three days the acidity of the media had reached p_H 3.7 regardless of the type of stool with which it had been inoculated. It is evident that acid producing organisms were present in both types of stools but that in the protein milk stool the conditions were not favorable for their proliferation, with the resultant production of acid. It seems

16. Grafe: München. Med. Wchnschr., 1914; quoted by Freudenberg, E., and Heller, O.: Jahrb. f. Kinderh. **96**:49, 1921.
17. Michaelis, L., and Marcora, F.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **14**:170, 1912.
18. Clark, W. M.: J. Biol. Chem. **22**:87, 1915.
19. Scheer, K.: Biochem. Ztschr. **130**:545, 1922.
20. Scheer, K.: Ztschr. f. Kinderh. **29**:253 (July) 1921.

probable then that the acidity of the stool is not the result of an infection by any particular type of organism, but rather the result of conditions which allow one or another definite type of organism to grow.

The reaction of the stool can be altered by the addition of certain inorganic substances to the diet. This has been demonstrated by Scheer and Muller,[21] who added alkaline sodium phosphate to breast milk and changed the reaction of the stool from p_H 5.0 to p_H 7.1. In the present paper, it is shown that the addition of a large amount of calcium carbonate may change the reaction of the stool (Chart 4). The explanation of the change is that the acids present react with these bases, and produce salts which have only a slight degree of acidity (buffer influence).

As already mentioned, the presence of proteins tends to produce an alkaline reaction on account of the production of ammonia by bacterial action. From the discussion so far, it would appear that the reaction of the stool depends on the ratio of the amount of carbohydrate present in the zone of fermentation on one hand, to the amount of protein and bases on the other hand. It has been shown that the type of carbohydrate may influence the acidity of the stool by being poorly absorbed in the upper part of the small intestine and thus reaching the zone of fermentation in fairly large quantities. Also, if the condition of the cells in the intestinal wall is such that they absorb the carbohydrate poorly, regardless of the type of carbohydrate in the food, then the amount of sugar available for fermentation would be increased, with a resultant increase in the acidity of the stool. In our opinion this is probably one of the most important factors in the production of acid in the intestinal canal.

There are at least two other factors which may be of considerable importance in determining the acidity of the stools. The first is the amount of intestinal secretion, which may have a marked effect on account of its alkaline reaction. The second is that in many pathologic conditions it is probable that the zone of fermentation extends farther up the intestinal canal than is normally the case.

It has been shown by Scheer [20] that there is enough carbohydrate present in protein milk to allow the production of an acidity of p_H 3.7 when inoculated with infants' stools. Consequently, if protein milk is fed to an infant, enough carbohydrate is being given to produce an acidity of p_H 3.7 if it is not absorbed before it reaches the zone of fermentation. It has been stated by Finkelstein [22] that at least 3 per cent. carbohydrate, and frequently more than this amount, should be present in the food in order to enable the metabolism of the body to

21. Scheer, K., and Muller, F.: Jahrb. f. Kinderh. **101**:143 (March) 1923.
22. Finkelstein, H.: Lehrbuch der Sauglings krankheiten, Berlin, Julius Springer, 1921, p. 291.

proceed in the normal manner. Then, if in an effort to correct an intestinal acidity an infant is fed protein milk with its low sugar and high protein and base content for a sufficient period to allow the low sugar to interfere with the nutrition of the intestinal cells, it is possible for the sugar to reach the zone of fermentation with the resultant production of acid. The addition of sugar to the diet might then stimulate the intestinal cells, so that there would be an increased absorption of the sugar and a resultant decrease in the acidity of the stool. Also, stimulation of the intestinal cells from the increased sugar content in the food might influence the amount of alkaline intestinal secretions and also the length of the zone of fermentation.

It is of interest to note the results obtained in the present investigation in the light of the above remarks. In Chart 2 we see that an infant fed on protein milk had stools with an acid reaction. The addition of sugar to the diet changed the reaction of the stool to the alkaline side of neutrality. A similar result is shown in Chart 3. This infant was on a diet containing 6.5 per cent. carbohydrate and the reaction of the stools was quite acid. The carbohydrate was increased to 18 per cent. and the stools promptly became more formed and had an alkaline reaction. Numerous other infants were fed whole soured milk with added carbohydrate up to a total content of 20 per cent., and in the majority of cases the stools were of a smooth and pasty consistency with a strongly alkaline reaction. A possible explanation for this surprising result is that the high carbohydrate so stimulated the intestinal cells that the absorption of sugar occurred very rapidly and thus lessened the opportunity for fermentation. The possibility must also be considered that the stimulated intestinal cells diminished the extent of the zone of fermentation and also produced a larger quantity of alkaline secretions. A further explanation might be found in the work of Wolff [23] who showed that when the concentration of sugar was greater than 10 per cent., fermentation was hindered.

The production of an acid stool by a parenteral infection may be explained on the ground that the vitality of the intestinal cells is diminished by the infection. This results in a lessened absorption of carbohydrate, and consequently an increase in the amount available for fermentation with the resultant production of acid. No doubt the zone of fermentation is also increased.

From the foregoing it might be assumed that we are advocating the use of high sugar diets in combination with whole soured milk to combat diarrheal conditions. While it is beyond the scope of this paper to enter into any discussion of this aspect of the problem, we simply draw attention to the fact that in certain diarrheal conditions the use of a

23. Wolff, E.: Ztschr. f. Kinderh. **31**:226, 1921.

concentrated high carbohydrate food will produce constipated alkaline stools. Similar results have been reported by Davidsohn and Rosenstein.[24] In many other cases, the use of this type of feeding will be followed by strongly acid watery stools and disastrous results.

SUMMARY

1. A simple procedure for the determination of the p_H of infants' stools has been described.

2. In the present investigation, over 1,300 determinations of the p_H of infants' stools have been made.

3. The p_H of stools from normal newly born breast fed infants was found to be singularly constant, varying from 4.7 to 5.1.

4. The acidity of stools from artificially fed infants was found to vary from p_H 4.6 to somewhat more alkaline than p_H 8.3.

5. An acidity as great as p_H 4.6 was encountered in artificially fed infants only in severe diarrheal conditions. Infants fed on buttersoup generally had stools with an acidity of about p_H 6.0. Infants fed on protein milk, cows' milk dilutions with added carbohydrates, and whole soured milk with added carbohydrates generally had stools more alkaline than p_H 7.0.

6. Whole soured milk, with added carbohydrates up to a total content of 20 per cent., generally produced strongly alkaline stools.

7. No difference was consistently observed in the acidity of the stool, whether the added carbohydrate was in the form of corn syrup, dextri maltose or cane sugar. In the present investigation, the effect produced by other sugars was not determined.

8. The degree of acidity of the stools was generally increased in the presence of parenteral infections.

9. Based on the present work and the work of others, the factors which influence the acidity of the stools have been discussed. From the chemical standpoint the acidity apparently depends on the ratio, *in the intestinal zone of fermentation*, of the carbohydrate on one hand to the protein and base on the other. The amount of carbohydrate in the zone of fermentation, apparently is influenced by the extent of the zone of fermentation, by the type of carbohydrate and by the state of health of the intestinal cells.

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24. Davidsohn, H., and Rosenstein, S.: Ztschr. f. Kinderh. **35**:207 (June) 1923.

THROMBOCYTOPENIC PURPURA HEMORRHAGICA SUCCESSFULLY TREATED BY SPLENECTOMY*

REPORT OF A CASE

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AND
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Our purpose in this report is to add another case to the small number of cases of thrombocytopenic purpura cured by splenectomy, in order to emphasize the extreme importance of this curative measure.

Kaznelson,[1] believing that essential thrombocytopenic purpura was due to the thrombolytic action of the spleen, had splenectomy performed as a curative measure. The result was very gratifying. The bleeding immediately stopped, and an extremely ill patient became rapidly converted into an apparently healthy person. Not only did the bleeding stop, but several of the pathologic phenomena, relating to blood coagulation characteristic of the disease, at once disappeared. Brill and Rosenthal, in New York, determined to make use of the same method, and obtained the same brilliant results.

We do not intend to discuss either the rationale of this surgical procedure nor to report on the literature and the pathogenesis of thrombocytopenic purpura. The reader interested is referred to recent articles by Brill and Rosenthal, American Journal of the Medical Sciences, October, 1923; Archives of Internal Medicine, December, 1923.

When a child entered the pediatric service with the clinical picture and hematologic findings characteristic of the thrombocytopenic form of purpura hemorrhagica, we decided on a splenectomy as a radical cure. The detailed case report is presented herewith.

REPORT OF CASE

History.—F. F., a girl, aged 8 years, of Italian parentage, was admitted to the Pediatric Service of Mount Sinai Hospital on July 19, 1923. The patient's chief complaints were that for the last three years she had had many epistaxes, and that ecchymoses frequently appeared on the body.

The family history was negative, there were no other members who showed any tendency to hemorrhage. Four brothers and one sister are alive and well. The past history was also negative, the patient never having been sick until the present illness.

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* Received for publication, Jan. 21, 1924.

* From the pediatric service of Mount Sinai Hospital.

1. Kaznelson: Wien. klin. Wchnschr. **29**:1451, 1916; Ztschr. f. klin. Med. **87**:133, 1919.

Present Illness.—For the last three years the child has had many epistaxes. These last from one day to several weeks. They come on suddenly, spontaneously and usually require nasal packing. On the least trauma, and at times apparently spontaneously, ecchymoses appear on the skin. For the last six weeks there has been a daily nosebleed. She has had several convulsions during the last three years, the latest one seven months ago. The stools are black only after nosebleeds. There was no hematemesis. The patient suffered from transient febrile periods. There was no palpitation or dyspnea.

Physical Examination.—The patient's general condition was good. She was pale, but did not appear acutely ill. The skin showed many black and blue spots of various sizes scattered over the surface of the body. The mucous surfaces were pale; the nasal mucosa failed to show any ulcerations or dilated veins. The lymph nodes were not palpable. The heart was not enlarged. There was a faint systolic murmur heard over the pulmonic area. The lungs were normal. The spleen was just felt at the costal border. The liver, felt 3 cm. below the costal border, was smooth and of normal consistency. The abdomen was soft, no masses were felt. The urine was normal. The blood Wassermann test was negative.

Blood Examination.—Hemoglobin, 60 per cent., red cells 5,200,000; white cells 4,800; polymorphonuclear neutrophils 58 per cent., lymphocytes 42 per cent.; bleeding time, twenty minutes; coagulation time, four minutes; tourniquet test positive. Clot retraction was absent (even after six hours); reticulated cells, 5.2 per cent.; platelets 11,000.

During the time the patient was under our observation there was blood continually oozing from the nares, and many new ecchymotic spots appeared. Splenectomy was decided on and performed, July 31, by Dr. Harold Neuhof. The child stood the operation very well but on the following day developed a right lower pneumonia. For four days she had fever and appeared sick, becoming slightly icteric on the third day. Eventually the temperature disappeared and the signs in the chest cleared up. She made an uneventful recovery, and was discharged from the hospital September 14.

Pathologic Report.—Macroscopically, the specimen consisted of a spleen, weighing 180 gm. and measuring 9.4 by 4.4 cm. It appeared to be about normal in size or perhaps slightly increased for the age of this patient (8 years). The hilum did not contain any hemolymph nodes. The surface was smooth and glistening, the cut surface appeared normal. Malpighian bodies appeared normal.

Pathologic Diagnosis.—Slight hypertrophy of Malpighian bodies. Infiltration of pulp with polymorphonuclear neutrophils and eosinophils.

The table shows a list of the blood examinations taken during and following the patient's stay in the hospital.

The foregoing history shows that we were dealing with a typical case of chronic hemorrhagic purpura with marked reduction in the number of the platelets. Not only the history of chronic bleeding but also the laboratory findings were characteristic, there was markedly prolonged bleeding time; coagulation was normal; clot retraction was absent; the platelets were greatly diminished; the white cells were morphologically normal and present in normal numbers. Experience having shown that cases of this nature were cured by splenectomy, we decided on operation, especially as the patient had been under medical treatment for three years without any beneficial results. The splenec-

Blood Examinations During and Following Patient's Stay in Hospital

	July 20	July 26	July 31 Before Operation	July 31 One Hour Post-operative	Aug. 1	Aug. 4	Aug. 6	Aug. 7	Aug. 8	Aug. 9	Aug. 20	Sept. 1	Oct. 20	Dec. 10
Hemoglobin (Sahli)	60%	60%	60%	60%	60%	56%	57%	50%	58%	61%	75%	80%	80%	85%
Red blood cells	5,200,000	5,400,000	4,500,000	4,500,000	5,600,000	4,800,000	4,800,000	4,300,000	4,300,000	4,400,000	.....	.....	.....	.....
White blood cells	4,800	8,300	.....	21,600	42,600	16,800	17,400	28,600	17,800	18,600	9,600	.....	.....	.....
Polymorphonuclears	58%	.....	.....	87%	91%	80%	78%	89%	85%	75%	60%	.....	.....	.....
Lymphocytes	42%	.....	.....	10%	6%	8%	6%	5%	8%	17%	23%	.....	.....	.....
Eosinophils	.....	.....	.....	.....	.....	.....	10%	3%	4%	7%	9%	.....	.....	.....
Mononuclears	.....	.....	.....	3%	3%	3%	6%	3%	3%	1%	8%	.....	.....	.....
Platelets	11,000	2,000	.....	42,000	80,000	220,000	120,000	90,000	90,000	100,000	100,000	90,000	90,000	60,000
Reticulated reds	5.2%	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
Bleeding time	20 min.	15 min.	16 min.	5 min.	1 min.	1½ min.	1 min.	2 min.	1½ min.	1½ min.	1½ min.	1½ min.	1 min.	1 min.
Coagulation time	4 min.	.....	.....	5 min.	7 min.	.....	.....	.....	.....	.....	.....	.....	.....	.....
Tourniquet test	Positive	.....	.....	Positive	Slightly positive 2 petechiae	.....	.....	Negative	.....	.....	.....	Negative	Negative	Negative
Clot retraction	Absent after 6 hrs.	.....	Absent after 24 hrs.	Absent 4 hrs., v. slight 24 hrs.	Positive in 1½ hrs.	.....	.....	Positive in 1 hr.	.....	.....	.....	.....	Positive in 1 hr.	Positive in 1 hr.

tomy was followed by a postoperative pneumonia, after which the child made an uninterrupted recovery.

Not only the change in the clinical condition but the immediate and later changes in the hematologic findings were of great interest. Before operation all the laboratory findings characteristic of this disease were present, the bleeding time was twenty minutes (normal from one to three minutes); the coagulation time was four minutes (normal); clot retraction was absent even after six hours (normal in one hour); the capillary resistance test of Hess was present, petechiae rapidly appearing on the skin of the forearm when the sphygmomanometer cuff was applied to the arm; the blood platelets were reduced as low as 2,000 per millimeter (normal 250,000). Curiously enough, in spite of the continued hemorrhages, there was present only a mild anemia, the red cells being normal in number, the hemoglobin being 60 per cent. One hour after the spleen had been removed the bleeding time had decreased to five minutes, twenty-four hours later it had decreased to one minute. It remained at from one to one and one-half minutes, from that time on, being still the same five months after operation. Clot retraction appeared twenty-four hours after splenectomy and has been present ever since. The tourniquet test was negative one week after operation and has remained so. The blood platelets counts were as follows: Before operation, 2,000, one hour after operation, 42,000, twenty-four hours postoperative, 80,000, on the fourth day, 220,000, after three weeks, 100,000, after three months, 90,000, the hemoglobin which was 60 per cent. before operation, rose to 85 per cent., at which it has remained. The bleeding stopped completely and the patient has been perfectly well since the operation five months ago.

ACUTE PELVIC ABSCESS IN CHILDREN *

REPORT OF TWO CASES RUPTURING INTO THE VAGINA

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A review of pediatrics and surgical literature indicates that acute pelvic abscess in infants rupturing through the vagina is rare. The following two cases were observed.

REPORT OF CASES

CASE 1.—A girl, aged 2 months, was the fourth child, of normal birth, and breast fed. The patient had been healthy from birth except for frequent stools. One day suddenly and without apparent cause she became fretful and developed a temperature of 103. Forty-eight hours later the mother noticed a profuse, greenish vaginal discharge, without odor, which persisted for about five days. With the appearance of the discharge the temperature became normal and the child was apparently well. About six weeks later, she again became fretful and feverish. With the appearance of a similar vaginal discharge she apparently felt well. After another interval of three months, during which time the child gained in weight normally and seemed to be in perfect health, the cycle of fever and discharge, followed by relief of symptoms, appeared. The discharge this time was much less copious, persisting, however, for about six days. Physical examination was always negative for any pathologic findings, except that during the time of the discharge pressure exerted deep in the pelvis behind the bladder brought an increase in the vaginal flow and at times even a spurt of pus from the vagina could be produced. No abdominal or pelvic mass was palpable. The vaginal discharge was definitely a greenish-yellow, odorless pus. No gonococci were found but staphylococci and pyocyaneus were present. Rectal examination was negative. The diagnosis was pelvic abscess of unknown origin, which ruptured spontaneously into the genital tract. The child is now 10 months old and apparently well.

CASE 2.—A girl, aged 9 months, entered the service of Dr. Julius H. Hess on March 23, 1922, with a history of restlessness and elevation of temperature for one week. The patient cried considerably. The temperature at one time was 105. The right ear drum had been incised four days previous to entrance.

Physical examination disclosed a very irritable baby. There was a purulent discharge from the right ear and the left ear drum was bulging. The throat was markedly injected. There were no other abnormal findings. The white blood count was 23,000, of which 56 per cent. were neutrophils, 32 per cent. small mononuclears and 12 per cent. large mononuclears. Hemoglobin was 70 per cent. and red blood count 3,800,000. The left ear drum was incised. Both ears discharged freely, but the temperature persisted, with daily rises as high as 103.

April 19, the parents insisted on taking the patient home. At the time of release the baby had a rectal temperature of 106.6, white blood count 15,000,

* Received for publication, Jan. 21, 1924.

the ears were discharging only slightly and the glands of the neck were not enlarged. It was difficult at this time to account for the temperature A few days later the child became worse. The parents called in their family physician, Dr. Lebowitz, to whom we are indebted for the subsequent history. The child seemed ill, and apparently in pain, the right thigh was held flexed on the abdomen and efforts to extend the limb were painful. The leg was edematous. A roentgen-ray examination was made of the right hip and at the same time the abdomen was fluoroscoped. A mass was seen in the right flank. During the manipulations, the right thigh was slightly extended and suddenly a gush of pus issued from the vagina. Prompt and complete recovery followed. There has been no recurrence to date.

Here again we were dealing with a pelvic abscess of unknown origin, which ruptured spontaneously into the vagina.

Griffith says most frequent forms of localized peritonitis is that associated with appendicitis. Its presence is also to be suspected whenever a child with gonorrheal vulvovaginitis suddenly develops fever with abdominal pain, tenderness and distention. He had seen this in but two instances.

Stoos [1] states that the etiology of localized peritonitis is somewhat different in infants than in older children. Appendicitis, the most frequent cause in children over 2 years, is rare in the first year of life, as is also encapsulated pneumococcus peritonitis.

Hertzler [2] states that localized pneumococcic peritonitis is more frequent in girls, occurring in forty-five out of fifty-two cases. Only five cases of ruptured pneumococcic peritonitis are reported and those through the umbilicus.

Nothnagel,[3] in speaking of appendicitis and spontaneous cures, states that perforation may occur into the ascending colon, ileum, rectum and even into the duodenum. Perforation into the bladder is rare and into the vagina still rarer. Perforation into the uterine cavity, reported by Langheld, is a pathologic curiosity.

Ashby speaks of general and localized peritonitis development from infected retroperitoneal glands which break down. These we feel may be the cause in our cases.

McCartney [4] brings out the fact experimentally in monkeys, that pneumococcic peritonitis arises from vaginal infections, as they occur in girls, and usually not before the age of 3 years. These again are different from our cases, ours being in infants under 1 year, and rupturing spontaneously.

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1. Stoos, U.: Pflaundler Schlossmann, Philadelphia, J. B. Lippincott Company, 1912, p. 251.
2. Hertzler: The Peritoneum, St. Louis, C. V. Mosby Company, 1919, p. 169.
3. Nothnagel: Diseases of the Peritoneum, Philadelphia, W. B. Saunders Company, 1905, p. 868.
4. McCartney, J. E.: Pathogenesis of Primary Pneumococcal Peritonitis, Brit. J. Pathol. & Bacteriol. **26**:507 (Oct.) 1923.

In connection with these cases the following two cases might be of interest in explaining the etiology of some of these abscesses.

REPORT OF CASES

CASE 1.—A girl, aged 5 years, was brought into the Sarah Morris Hospital on the service of Dr. Hess because of abdominal pain, painful urination and poor appetite. The patient was apparently well until two weeks previous to admission to the hospital, when she commenced to complain of painful urination. There was a slight frequency but no blood or gravel was noticed in the urine. Nausea was present at the onset but later subsided. The condition became progressively worse and was accompanied by a daily rise in temperature. One week previous to admission the child complained of a severe abdominal colic and pointed to the left lower quadrant. The bowels were regular but the appetite was very poor. The patient had scarlet fever at the age of 2, and measles at 3 years of age. The family history was negative for tuberculosis.

Physical Examination.—At the time of admission examination revealed a well-developed girl with flushed face, lying flat in bed with the right thigh flexed on the abdomen. The abdomen was tense all over but not distended. Rigidity and tenderness were present on both sides but most marked in the lower right abdominal quadrant. The temperature was 100.4, respiration 32. White blood count was 18,000, with 80 per cent. polymorphonuclears. The urine showed a faint trace of albumin with an occasional white blood cell. A definite mass was palpable just below the umbilicus, and a diagnosis of acute appendicitis with probable abscess formation was made and immediate operation advised.

At operation, the following conditions were noted: There was no free fluid in the abdomen. The appendix was slightly injected but clearly was not the cause of the symptoms. The mass, which had been noted previous to operation, could be definitely felt extending out of the pelvis from about the level of the promontory of the sacrum up to the abdominal wall. It was walled off by firm adhesions. A stab wound was made through the midline of the abdominal wall and a thick creamy, odorless pus flowed out, from which staphylococci were cultured. A finger was then introduced into the abscess cavity and a few partitions broken down. The first incision, which had been walled off, was closed and the abscess drained through the stab wound. The internal genitalia, on rectal examination after operation, appeared normal.

The patient made an uneventful recovery. The wound stopped draining in about two weeks, and she was discharged about a week later.

After the operation, careful roentgen-ray examinations were made of the spine and pelvis but no signs of bone destruction were noted. The diagnosis was pelvic abscess of unknown origin.

CASE 2.—A boy, aged 3 years, was admitted to the Sarah Morris Hospital, July 24, 1921, with a history of fever, soreness on the right side of abdomen and a "sore" mouth.

Twenty-two days previous to entrance, the patient awakened in the morning as usual, but was unable to stand because of pain in the right limb. He was able to move the limb voluntarily, however. The condition seemed to progress so that for five days before admission he was unable to stand at all. He had an elevation of temperature for several days, but the exact temperature was not taken. For four weeks he had "sores" in the mouth. The bowels were regular and the appetite was good up to the day before entrance. He had had no diarrhea or vomiting. There had been no previous illness, and the family history was negative.

Physical Examination.—The patient was a well-developed child, who held the right lower extremity in a flexed position. He could not extend it without pain. There was a mass in the lower abdomen on the right side, extending down to

above the hip joint and laterally in the flanks. Increased muscle rigidity and tenderness were present. On rectal examination no mass was palpable.

Roentgen-ray examination of the right hip was negative. The temperature was 99.6 rectal, pulse 120. White blood count was 27,000, of which 65 per cent. were neutrophils, 30 per cent. small mononuclears, 4 per cent. large mononuclears and 1 per cent. transitionals. The urine was negative. The Pirquet and Wassermann tests were negative.

An exploratory laparotomy was performed. The appendix was normal. A large, boggy retroperitoneal mass was palpated in the right lower quadrant. There was no definite fluctuation. The peritoneum was closed and the mass exposed by elevating the peritoneum. The mass was found to be composed of large swollen retroperitoneal glands. Inasmuch as infection was definitely present, no attempt was made to excise a piece for microscopic study. A small gutta-percha drain was left in the wound, and for a week there was a slight serous discharge.

The patient made an uneventful recovery, and went home at the end of two weeks, at which time the glands had disappeared and the child walked normally.

The probable etiology was the same as that of the stomatitis, which was present for four weeks previous to admission.

CONCLUSIONS

Three cases of acute pelvic abscess formation are reported, with relief of symptoms in each case after drainage. In the first two, this occurred spontaneously through the vagina and in the third case artificially by operation. In the third case the cause of the abscess was proved to be not the appendix, and it probably did not originate from the internal genitalia, which were palpated and found to be normal. The abscess possibly originated from the retroperitoneal structures and was presumably of glandular origin. The frequent association of abdominal pain with throat conditions in childhood, recently brought to our attention by Brennemann,[5] is known to us. Some pelvic abscesses might be from just such infections involving the lymph glands which break down. We are absolutely at a loss to explain the source otherwise. They were not appendiceal abscesses. These, of course, may rupture spontaneously but they almost invariably rupture into the bowel. A spondylitis might give rise to a pelvic abscess but no signs or symptoms pointing to spinal origin were present, nor in such cases would the patients be apt to recover spontaneously. The fact that all three cases occurred in female patients, and that in two there was a discharge of pus from the vagina, might point to the genitalia as the source. Pyosalpinx has been known to occur in infants, and must be considered as a possible etiologic factor.

5. Brennemann, Joseph: The Abdominal Pain of Throat Infections, Am. J. Dis. Child. **22**:493 (Nov.) 1921.

THE ESTIMATION OF THE VOLUME OF BLOOD IN NORMAL INFANTS AND IN INFANTS WITH SEVERE MALNUTRITION *

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No study on fluid regulation in the body can be complete without some knowledge of the total amount of circulating fluid. Because of the large quantities of blood hitherto necessary to estimate the blood volume, few determinations have been made in infants. It was primarily with the purpose of obtaining more data on the subject that this investigation was undertaken.

The method used for estimating the volume of blood was a micro-modification of the method of Keith, Rowntree, and Geraghty [1] as improved by Hooper, Smith, Belt and Whipple.[2] A known amount of a nontoxic, slowly diffusible dye is injected into a vein, is allowed to circulate for a few minutes and a specimen of blood withdrawn. By determining the concentration of the dye in the plasma, the plasma volume may be calculated. The total blood volume may be computed from the hematocrit reading.

In normal adults the total volume of blood is about 9 per cent. of the body weight, and the plasma volume about 5 per cent.[1] In normal infants Lucas and Dearing [3] found that the values were higher and varied much more widely than in adults. According to these observers, in the new-born the volume of blood varies from 10.7 to 19.5 per cent. of the body weight, averaging 14.7. The plasma volume varies from 4.2 to 7.7 per cent. of the body weight, averaging 5.9. In older infants the blood volume ranges from 9.0 to 12.6 per cent. of the body weight averaging 11.0. The plasma volume varies from 5.7 to 7.8 per cent. of the body weight, averaging 6.7.

Marriott and Perkins [4] determined the volume of blood in normal infants and in infants with marasmus. They found that in seven

* Received for publication, Jan. 23, 1924.

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1. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547 (Oct.) 1915.

2. Hooper, C. W.; Smith, H. P.; Belt, A. E., and Whipple, G. H.: Experimental Control of a Dye Blood Volume Method, Am. J. Physiol. **51**:205 (March) 1920.

3. Lucas, W. P., and Dearing, B. F.: Blood Volume in Infants Estimated by the Vital Dye Method, Am. J. Dis. Child. **21**:96 (Jan.) 1921.

4. Marriott, W. M., and Perkins, J. F. (quoted by Marriott): Some Phases of the Pathology of Nutrition in Infancy, Harvey Lectures, 1920-1921, p. 121.

normal infants the volume of blood varied from 8.0 to 10.8 per cent. of the body weight. In eleven infants with marasmus the values ranged from 4.0 to 10.4 per cent. of the body weight. They state that the higher values were obtained in infants who might be considered as convalescing from the marasmus. They conclude that the volume of blood in infants with marasmus is lower that in normal infants.

PROCEDURE AND METHODS

The blood volume was determined in a group of normal infants and infants with severe malnutrition. Estimations of the serum protein concentration and hemoglobin percentage were made at the same time.

Determinations were made from three to four hours after a feeding. To avoid diurnal variations the blood specimens were always taken at the same time of the day (between 1 and 2 p. m.). Specimens for hemoglobin and serum protein estimations were obtained immediately before the dye was injected. Hemoglobin was determined by the carbon monoxid method of Palmer.[5] The serum protein concentration was determined with the Abbe refractometer. The technic used was similar to that described in previous papers.[6] The calculations were made according to Reiss.[7]

The following micromodification of the dye method of Keith, Rowntree and Geraghty [1] was used to determine the volume of blood: A 1.5 per cent. solution of brilliant vital red in saline was prepared. This solution was sterilized before each set of determinations. Two cubic centimeters of blood were drawn into a dry syringe and delivered into a heavy walled hematocrit tube, 12.5 cm. in length and 0.6 cm. in diameter. The graduated tubes were calibrated in divisions of 0.04 c.c. and contained 0.4 c.c. of 1.6 per cent. sodium oxalate solution to prevent clotting. The oxalate and blood were mixed by inverting. The plasma obtained in this way was later used in the preparation of the standard.

Without removing the needle from the vein, 1 c.c. of dye, prepared in the manner described above, was injected.[8] Four minutes later a fresh needle was introduced and 2 c.c. of blood again withdrawn. The blood obtained in this way was delivered into a tube similar to the first and also containing 0.4 c.c. of sodium oxalate solution.

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5. Palmer, W. W.: The Colorimeter Determination of Hemoglobin, J. Biol. Chem. **33**:119 (Jan.) 1918.

6. Bakwin, H.: Dehydration in New-Borns, Am. J. Dis. Child. **24**:497 (Dec.) 1922.

7. Reiss, E.: Die refraktometrischen Untersuchungen und ihre Ergebnisse für die Physiologie und Pathologie des Menschen, Ergebn. d. inn. Med. u. Kinderh. **10**:531, 1913.

8. The amount of dye used for injection may be varied according to the weight of the subject. The variation in the weight of the babies studied was comparatively small, and we therefore used 1 c.c. except in infants under 3 kg. in whom 0.5 c.c. was used.

Both tubes were then centrifuged for twenty minutes at 1,500 revolutions per minute and hematocrit readings made in the tubes. The supernatant fluid (plasma and oxalate solution) was pipetted off into clean test tubes. One cubic centimeter of the dye-stained plasma oxalate mixture was added to 2 c.c. of normal saline and matched in a colorimeter (using microcups and microplungers) against the standard mixture. The standard mixture consisted of 1 c.c. of saline, 1 c.c. of plasma oxalate solution obtained before the dye was injected and 1 c.c. of dilute dye solution.[9] The dilute dye solution was prepared by making up 1 c.c. of 1.5 per cent. dye solution to 400 c.c. with saline. This was prepared before each set of determinations.

The calculations were as follows:

$$\text{Plasma volume} = \frac{R}{15} \times 400 \times \frac{P - 0.4}{F} \times D$$

$$\text{Blood volume} = \frac{\text{plasma volume}}{\text{plasma per cent.}} \times 100$$

Corpuscular volume = blood volume minus plasma volume

where

R = colorimeter reading with the standard at 15.

P = amount of dye-stained plasma oxalate solution in the hematocrit tube.

D = c.c. of dye injected.

$$\text{Plasma per cent.} = \frac{P - 0.4}{\text{Total amount of fluid in tube minus } 0.4} \times 100$$

This is probably as accurate as the original method, since the errors due to measuring the smaller amounts of fluid are well within the limits of error inherent in the method.[10]

The longitudinal sinus was used in all the determinations. A short beveled, 20 gage needle, 6 mm. in length, proved entirely satisfactory.

All the babies used in this study were artificially fed. It was not possible to obtain a large series of strictly normal babies. The "normal"

9. In the experiments of Lucas and Dearing,[8] sodium oxalate solution was added to the tube containing the blood obtained before the dye was injected but not to the second tube. The actual amount of plasma in their standard tubes was therefore from 25 to 40 per cent. less than in the "unknown" tube. We have found that even small discrepancies in the actual amount of plasma added causes difficulty in the colorimeter reading. The plasma of the new-born is often high colored. In older infants turbid serums are not infrequently encountered.

10. The exact manner in which the dye is removed from the body is unknown. Keith, Rowntree and Geraghty, using vital red, found small amounts in the urine. With the specimen used in these experiments (brilliant vital red) the urine was always negative. In the feces, however, dye was regularly present, in one instance as early as ten hours after the injection and as late as eleven days afterward.

babies were healthy in the sense that they were not suffering from any acute illness. Some of them were slightly underweight. None of the babies had fever.

RESULTS

Repeated determinations of the blood, plasma and corpuscular volumes on the same patient were made in sixteen instances (Table 1). Two of the infants were markedly underweight (Cases 537, 542). Two others were anemic (Cases 548, 549). The rest of the babies were fairly normal.

TABLE 1.—*The Results of Repeated Determinations of the Blood Volume, Etc., in Infants.*

			Total Volume			Volume per Kg. Body Weight				
Case	Age, Months	Weight, Kg.	Blood, C.c.	Plasma, C.c.	Corpuscles, C.c.	Blood, C.c.	Plasma, C.c.	Corpuscles, C.c.	Hemoglobin, Gm. per 100 C.c.	Serum Protein, per Cent.
504	¾	3.47	344	204	140	99	59	40	12.9	—
	1½	3.46	334	214	120	97	62	35	11.2	—
505	1	2.76	353	198	155	128	71	57	14.3	—
	1½	2.93	281	178	103	96	61	35	11.7	—
	3½	3.93	372	243	129	94	61	33	—	—
506	1½	2.78	413	185	228	148	66	82	16.8	—
	1¾	3.04	360	190	170	117	63	54	13.8	4.90
513	2	3.72	401	272	129	108	69	39	11.7	5.49
	3	4.20	377	242	135	90	58	32	10.4	—
532	2	2.79	326	210	116	117	75	42	9.5	5.31
	2½	2.82	364	236	128	129	84	45	11.2	—
510	2	3.47	325	228	97	94	66	28	9.9	5.31
	4	3.58	403	258	145	113	72	41	12.9	—
537	3	2.93	334	216	118	115	74	41	10.3	5.95
	3½	2.93	347	218	129	118	74	44	11.2	—
536	3	2.87	353	242	111	126	85	41	—	7.11
	3½	2.98	366	248	118	123	83	40	9.0	6.53
	3¾	3.38	396	250	146	117	74	43	12.6	6.53
519	3½	3.90	434	270	164	112	69	43	12.5	7.11
	3¾	4.32	452	282	170	105	65	40	—	—
517	3½	4.35	437	284	153	101	65	36	10.1	—
	4	4.52	403	272	131	89	60	29	9.7	5.84
523	5	5.48	457	290	167	83	53	30	10.5	—
	5½	5.77	524	344	180	91	60	31	10.6	6.17
	6	6.03	517	326	191	86	54	32	—	—
	6½	6.17	575	359	216	93	58	35	10.7	6.59
542	5	2.90	228	161	67	79	56	23	9.2	5.78
	5½	2.90	276	185	91	95	64	31	9.6	5.89
	6	3.04	294	206	88	97	68	29	10.1	6.24
	7	3.41	342	238	104	100	70	30	9.8	—
524	5½	5.12	479	303	176	94	59	35	11.8	—
	5¾	4.97	520	327	193	105	66	39	12.7	—
546	6½	4.67	444	302	142	95	65	30	8.6	7.79
	7½	4.66	483	314	171	104	67	37	10.7	7.93
	7¾	4.88	503	326	177	103	67	36	9.7	7.56
548	7	3.41	300	225	75	88	66	22	7.2	—
	7½	3.54	422	308	114	115	85	30	8.1	—
549	9	4.80	446	334	112	93	70	23	5.2	6.87
	9½	4.83	467	356	111	97	74	23	6.1	7.17

In the three infants under 8 weeks of age on whom repeated determinations were made (Cases 504, 505, 506) a drop in the absolute volume of corpuscles occurred. In Case 505, despite the fact that the baby gained 170 gm. in two weeks, the volume of red cells fell from 155 c.c. to 103 c.c. In Case 506, similarly, though the baby gained 250 gm. in weight during the week intervening between the two determinations, the volume of red cells fell from 228 c.c. to 170 c.c. In the only

infant under 8 weeks of age on whom Lucas and Dearing made repeated determinations (their Table 4, Case B. O.) a similar drop in the absolute volume of red cells from 175 c.c. to 134 c.c. occurred.

The volume of plasma in our cases showed little change during this period of life. It increased slightly in two cases and fell slightly in the third. In the patient studied by Lucas and Dearing there was a considerable increase in the plasma volume between the fifteenth and fiftieth days.

In all four infants the fall in red cell volume was accompanied by a drop in the hemoglobin percentage. It is known that the red cell count during this period falls rapidly. These results indicate that the fall in the hemoglobin percentage and red cell count during the first weeks of life is owing to an actual reduction in the number of circulating corpuscles and not to an increase in the plasma volume.

After the first weeks of life the volume of plasma and corpuscles increases steadily. It is interesting to note that this usually proceeds even though no significant gain in weight occurs (Table 1, Cases 532, 537, 542, 524, 546, 549).

The Relation Between the Volume of Blood and the Body Weight in Normal Infants.—A résumé of the results of estimations of the volume of blood, plasma and red cells together with other data is given in Table 2. In Charts 1, 2 and 3 the blood, plasma and corpuscular volumes per kilogram of body weight, respectively, are graphically represented in relation to age. The dots represent individual determinations. The continuous lines in Charts 1, 3, 4 and 6 represent the average at different ages as obtained by the method of least squares.

The volume of blood per kilogram of body weight in normal infants varies from 71 c.c. to 148 c.c., averaging 101 c.c. The values obtained, like those of Lucas and Dearing, are not only higher than in adults but they vary more widely. It is of interest that the highest figures were obtained during the new-born period (Chart 1). There is a gradual fall as the age increases but at 7 months the blood volume is still relatively higher than in adults. The variations in results are also more marked during the new-born period than later in infancy.

That the decrease in the amount of blood per kilogram of body weight as the age increases is due to a diminution in the volume of red cells is apparent from Charts 2 and 3. The volume of red cells is relatively high during the first weeks of life. It falls, abruptly at first, more gradually later, the curve for the corpuscular volume running in a general way parallel to that of the total blood volume.

The volume of plasma per kilogram of body weight (Chart 2) shows wide variations (38 c.c. to 72 c.c., averaging 61 c.c. per kilogram of body weight) particularly during the new-born period. This is

in marked contrast to the relative constancy of the plasma volume in adults.[11] Recent studies tend to show that, in adults of the same nutritional condition, despite wide variations in the volume of corpuscles, the plasma volume remains fairly constant. Bock [11] points out that even in such widely different conditions as polycythemia and pernicious anemia, though the red cell volume varies greatly, the plasma volume remains relatively unchanged.

TABLE 2.—*The Blood Volume in Normal Infants*

			Total Volume			Volume per Kg. Body Weight				
Case	Age	Weight, Kg.	Blood, C.c.	Plasma, C.c.	Corpuscles, C.c.	Blood, C.c.	Plasma, C.c.	Corpuscles, C.c.	Hemoglobin, Gm. per 100 C.c.	Serum Protein, per Cent.
500	12 days	2.40	253	91	162	105	38	67	19.4	—
501	2 wks.	3.04	358	222	136	118	73	45	12.8	5.49
502	2 wks.	2.84	304	152	152	107	54	53	—	6.01
503	3 wks.	3.60	402	186	216	113	52	61	18.4	5.78
504	3 wks.	3.47	344	204	140	99	59	40	12.9	—
505	1 mo.	2.76	353	198	155	128	71	57	14.3	—
518	5 wks.	2.78	294	161	133	106	57	48	13.8	5.14
504	5 wks.	3.39	386	211	175	114	62	52	13.3	5.78
504	5 wks.	3.46	334	214	120	97	62	35	13.1	—
506	6 wks.	2.79	413	185	228	148	66	82	16.8	—
505	6 wks.	2.93	281	178	103	96	61	35	11.7	—
509	6 wks.	3.64	372	244	128	102	67	35	10.3	6.30
506	7 wks.	3.04	360	190	170	117	62	54	13.8	4.90
510	2 mos.	3.47	325	228	97	94	66	28	9.9	5.34
511	2 mos.	4.85	448	282	166	93	58	34	11.3	5.66
512	2 mos.	4.09	299	206	93	73	50	23	—	—
513	2 mos.	3.72	401	272	129	108	69	39	11.7	5.49
513	3 mos.	4.20	377	242	135	90	58	32	10.4	—
514	3 mos.	3.42	368	236	132	108	69	39	12.7	5.37
515	3 mos.	4.83	453	310	143	94	64	30	10.4	5.95
517	3 mos.	4.35	437	284	153	101	65	35	10.1	6.70
505	3 mos.	3.98	372	243	129	94	61	33	—	—
519	3 mos.	3.90	434	270	164	112	69	43	12.5	7.11
519	4 mos.	4.32	452	282	170	105	65	40	—	—
510	4 mos.	3.58	403	258	145	113	72	41	11.4	—
517	4 mos.	4.52	403	272	131	89	60	29	9.7	5.84
521	5 mos.	5.38	515	320	195	96	60	36	10.6	7.11
505	5 mos.	4.99	478	303	175	96	61	35	12.8	5.37
522	5 mos.	5.48	457	290	167	83	53	31	10.5	—
523	5½ mos.	5.77	524	344	180	91	60	31	10.6	6.07
524	5½ mos.	5.12	479	303	176	94	59	35	11.8	....
524	5¾ mos.	4.97	520	327	193	105	66	39	12.7	....
523	6 mos.	6.03	517	326	191	86	54	32	....	....
523	6½ mos.	6.17	575	359	216	93	58	55	10.7	6.59
525	7 mos.	5.62	408	270	138	71	48	23	—	6.65
528	10 mos.	6.53	534	320	114	82	49	33	9.4	—

It is probable that these wide variations in the relation between plasma volume and body weight in infants are due, in part at least, to the fact that the daily up and down fluctuations in the weight curve of an artificially fed infant do not represent the true weight of the baby but are due to changes in the water content of the tissues. Freund [12] studied the nitrogen and chlorin balance in a series of artificially fed infants and found that during days of rapid weight gain the nitrogen retention was sufficient to account for only a small part of the gain.

11. Bock, A. V.: The Constancy of the Volume of the Blood Plasma, Arch. Int. Med. **27**:83 (Jan.) 1921.

12. Freund, W.: Wasser und Salze in ihren Beziehungen zu den Körpergewichtsschwankungen der Säuglinge, Jahrb. f. Kinderh. **59**:421, 1904.

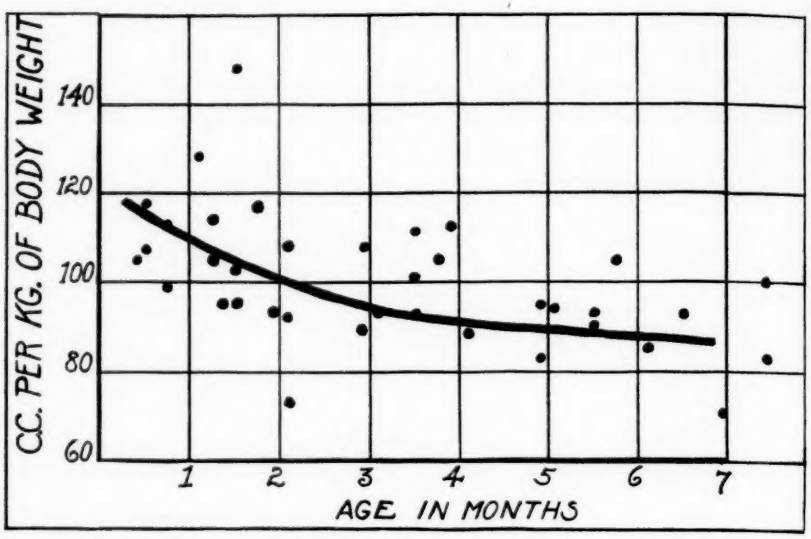

Chart 1.—The volume of blood per kilogram of body weight in relation to age in normal infants.

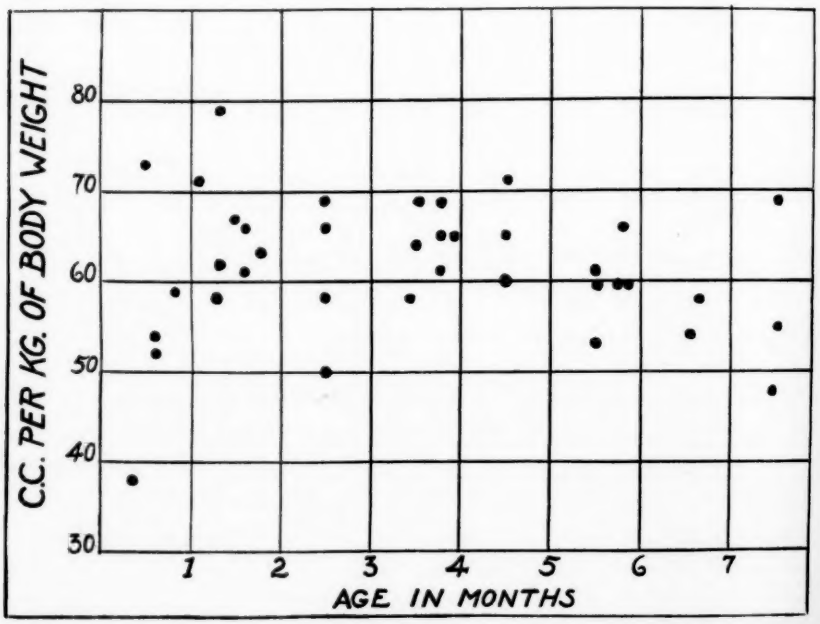

Chart 2.—The volume of plasma per kilogram of body weight in relation to age in normal infants.

That the major part of the weight increase was due to water retention was shown by a marked diminution in the elimination of chlorid and alkali salts. Moreover it has been found [13] that rapid weight increases in artificially fed infants are not accompanied by an increase in the water content of the plasma, thus indicating that the increased amount of fluid is held in the tissues and does not enter the blood.

TABLE 3.—*The Blood Volume in Infants with Severe Malnutrition*

			Total Volume			Volume per Kg. Body Weight				
Case	Age, Months	Weight, Kg.	Blood, C.c.	Plasma, C.c.	Corpuscles, C.c.	Blood, C.c.	Plasma, C.c.	Corpuscles, C.c.	Hemoglobin, Gm. per 100 C.c.	Serum Protein, per Cent.
529	2	2.61	282	171	111	108	66	42	6.44	6.53
530	2	2.99	276	182	94	92	61	31	10.0	6.24
531	2	2.80	235	153	82	84	54	30	—	—
532	2	2.79	326	210	116	117	75	42	9.53	5.31
532	2½	2.82	364	236	128	129	84	45	11.2	—
533	2½	3.04	330	244	86	109	81	28	8.5	5.25
534	3	3.18	325	214	111	105	67	38	10.7	5.43
536	3	2.87	353	242	111	126	85	41	—	7.11
537	3	2.98	334	216	118	115	74	41	10.3	5.95
537	3½	2.98	347	218	129	118	74	44	11.2	—
538	3½	3.97	314	204	110	79	51	28	9.6	5.95
536	3½	2.98	366	248	118	123	83	40	9.0	6.53
536	3¾	3.38	396	250	146	117	74	43	12.6	6.53
576	4	3.10	308	209	99	99	67	32	10.4	—
577	4	4.00	387	255	132	97	64	33	11.38	5.89
539	4	4.00	468	312	156	117	78	39	11.1	6.24
540	4½	4.80	405	272	133	84	57	27	10.0	7.11
541	5	4.00	490	313	177	123	79	44	10.7	6.36
542	5	2.90	228	161	67	79	56	23	9.2	5.78
542	5½	2.90	276	185	91	95	64	31	9.6	5.89
542	6	3.04	294	206	88	97	68	28	10.1	6.24
543	6	3.64	354	225	128	97	62	35	10.2	7.52
544	6	3.58	366	250	116	102	70	32	12.8	5.37
545	6	4.54	401	269	132	88	59	29	9.4	6.36
546	6½	4.67	444	302	142	95	65	30	8.6	7.79
547	7	4.60	390	252	138	84	55	29	7.87	4.85
526	7	4.09	341	224	117	84	55	28	10.4	—
542	7	3.41	342	238	104	100	70	30	9.8	—
548	7	3.41	300	225	75	88	66	22	7.17	—
548	7½	3.64	422	308	114	115	85	30	8.05	—
549	7½	4.35	437	298	139	101	69	31	9.1	6.81
546	7½	4.66	483	314	169	104	67	37	10.7	7.93
546	7¾	4.88	503	326	177	103	67	36	9.7	7.56
567	9	4.30	493	306	187	115	71	44	11.1	7.05
559	9	4.80	445	334	111	93	70	23	5.2	6.87
559	9½	4.83	467	356	111	97	74	23	6.1	7.17
550	12	5.10	553	338	215	108	66	42	9.7	7.11
551	14	3.50	309	221	88	88	63	25	7.9	4.07
552	14½	3.05	325	224	101	107	74	33	—	6.12
553	15	6.24	630	420	110	101	67	34	—	7.81

The Volume of Blood in Infants with Severe Malnutrition.—A résumé of the results in infants with severe malnutrition is given in Table 3. In Charts 4, 5 and 6 the blood, plasma and corpuscular volumes, respectively, per kilogram of body weight are represented according to age. The crosses indicate individual determinations in marantic babies. The dots in Chart 5 represent individual determinations in normal babies and are inserted for comparison. The heavy continuous lines in Charts 4 and 6 are transcribed from Charts 1 and 3

13. Bakwin, H.: The Water Content of Infants' Blood During Periods of Rapid Increase in Weight, Am. J. Dis. Child. **25**:406 (May) 1923.

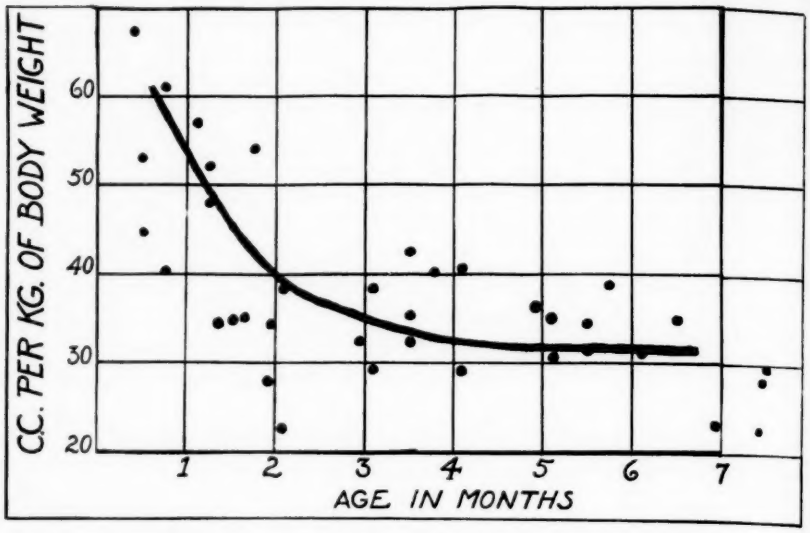

Chart 3.—The volume of red cells per kilogram of body weight in relation to age in normal infants.

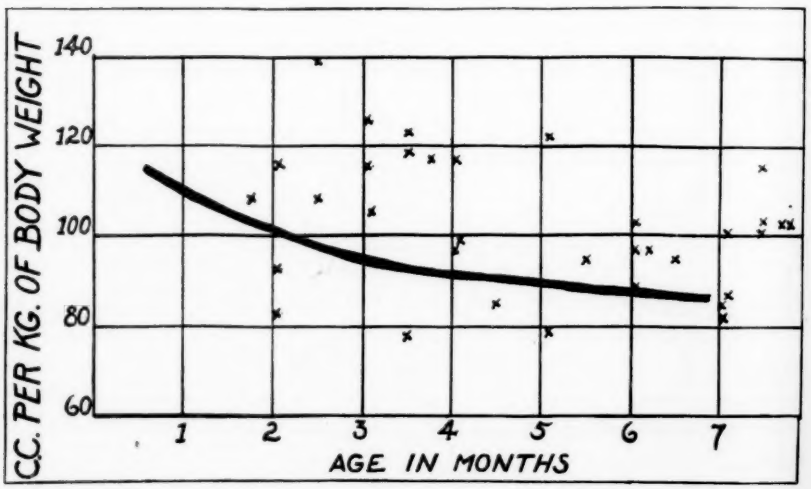

Chart 4.—The volume of blood per kilogram of body weight in relation to age in infants with severe malnutrition.

and represent the averages for the blood and red cell volumes per kilogram of body weight at different ages as obtained by the method of least squares.

The average value obtained for the infants with severe malnutrition varies little from the normal average (103 c.c. of blood per kilogram of body weight for infants with marasmus, 101 c.c. for normal infants). However, since, in computing the normal average, the values obtained in infants during the first weeks of life when the blood volume is high were included, the averages for normal and marantic infants are not directly comparable. Most of the normal babies were under 4 months, whereas most of the marantic infants were past this age. For the same age period the blood volume in infants with marasmus is relatively higher than in normal infants (Chart 4). This is true in spite of the fact that most of the infants with marasmus were more or less anemic (hemoglobin under 10 gm. per hundred cubic centimeters of blood), a factor which would tend to lower their blood volume.

The plasma volume in marantic infants is relatively higher than in normal infants. The average value for the plasma volume in infants with marasmus is 69 c.c. per kilogram of body weight, for normal infants 61 c.c.

The Relation Between the Volume of Blood and the Body Surface in Infants.—According to Dreyer and Ray [14] the volume of blood in mammals is proportional to the body surface and not to the body weight. They believe that the practice of expressing the blood volume in percentage of body weight is misleading, particularly when individuals of different nutritional conditions are compared. Since adipose tissue is comparatively nonvascular, thin individuals of the same length and muscular development should have a larger blood volume in relation to the body weight than fat individuals. The bodies of the infants with malnutrition obviously contained less fat than normal babies, and one would therefore expect them to have a higher blood volume in relation to body weight than normal infants.

The blood volume was computed in relation to body surface [15] in nineteen cases. Whereas in adults the amount of blood per square meter of body surface averages 3.12 liters,[16] the average value for infants is 1.7 liters. Though the blood volume in an infant, therefore, is large in proportion to the body weight it is much smaller than the adult in relation to body surface.

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14. Dreyer, G., and Ray, W.: Phil. Tr. Roy. Soc. London, **201**:133, 1910.

15. Dubois, D., and Dubois, E. F.: A Formula to Estimate the Approximate Surface Area if Height and Weight be Known, Arch. Int. Med. **17**:863 (June) 1916.

16. Keith, N. M.: The Total Circulating Volume of Blood and Plasma in Cases of Chronic Anemia and Leukemia, Am. J. M. Sc. **165**:174 (Feb.) 1923.

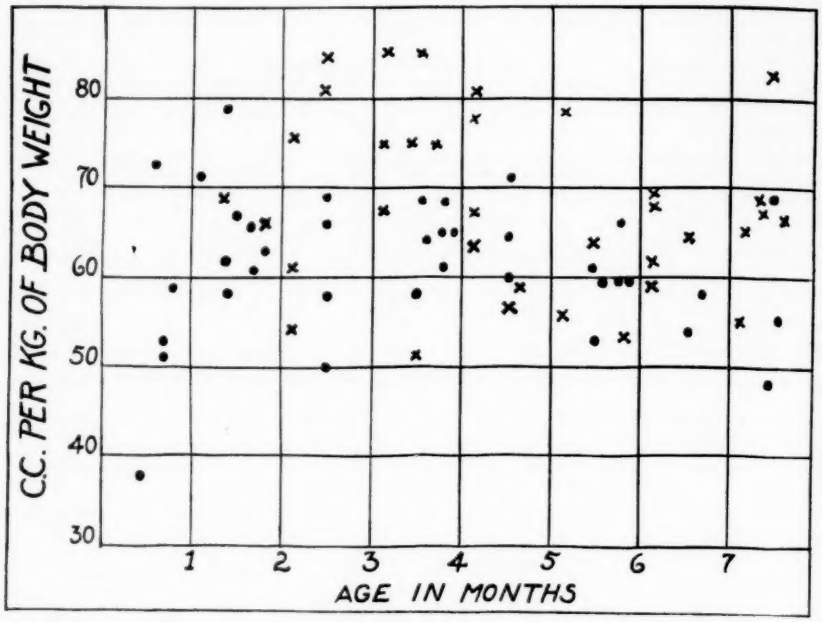

Chart 5.—The volume of plasma per kilogram of body weight in relation to age in infants with severe malnutrition.

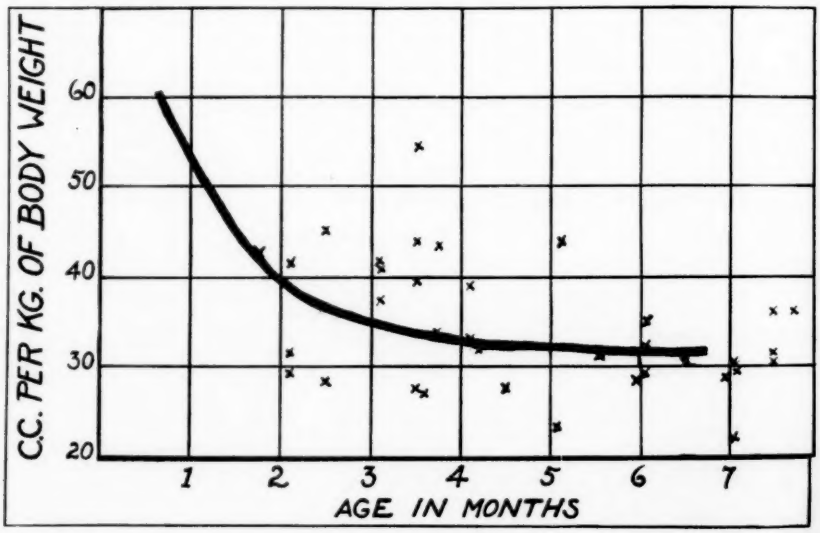

Chart 6.—The volume of red cells per kilogram of body weight in relation to age in infants with severe malnutrition.

The Relation Between the Serum Protein Per Cent. and the Plasma Volume.—No relation was found between the plasma volume per kilogram of body weight and the serum protein per cent.

SUMMARY AND CONCLUSIONS

1. A micromodification of the dye method of Keith, Rowntree, and Geraghty has been described, by which the volume of blood can be determined with 4 c.c. of blood.

2. At birth, the corpuscular volume is relatively high. It falls rapidly during the first weeks of life, so that the absolute volume of red cells is less at 8 weeks of age than at birth.

3. The volume of blood and plasma in infants is higher in relation to the body weight and varies more widely than in adults. The average value for the blood volume is 101 c.c. per kilogram of body wieght. The average value for the plasma volume is 61 c.c. per kilogram of body weight.

4. The volume of blood and plasma in marantic infants is higher than in normal infants.

5. The volume of blood per unit of body surface in infants is much smaller than in adults (1.7 liters per square meter for infants, 3.12 liters for adults).

A COMPARISON OF THE METABOLISM OF SOME MINERAL CONSTITUENTS OF COW'S MILK AND OF BREAST MILK IN THE SAME INFANT*

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It is an established fact that the mineral constituents of cow's milk are not so well utilized by infants as are those of breast milk. This fact, however, seems to have been based largely on investigations in which different infants were employed as subjects for the experiments on the two kinds of milk. It is a matter of surprise, on going through the literature, to see how little has been written regarding the mineral metabolism in the same infant fed on the two kinds of milk. Since the constitution of normal people is known to vary to a certain extent with different persons, the difference in the utilization of the mineral constituents of the two milks may be owing not only to the nature of the milk, but to the constitutional differences of the individual infants. In order to determine whether there is any difference in the utilization of mineral constituents of the two milks by the same infant, a series of metabolic studies was undertaken.

The first series of experiments was made on five apparently normal male infants between the ages of 11 days and 6 months. They were fed alternately with breast milk and modified cow's milk, six days on each diet, and analysis was made of the calcium, magnesium, phosphorus, and chlorid content of both urine and feces. On the first three days of each period no specimens were collected, thus giving an opportunity for the child to become adjusted to the change from one milk to the other. In changing from breast milk to cow's milk, feedings of cow's milk were substituted for breast feedings gradually, instead of making the complete transition at one time. The same procedure was followed in changing from cow's milk to breast milk. This prevented the onset of gastro-intestinal disturbances. Twenty-four-hour specimens of urine and feces were collected for three days after the diet was established.

* Received for publication, Jan. 23, 1924.
* From the Nelson Morris Memorial Institute for Medical Research, and the Sarah Morris Hospital for Children of the Michael Reese Hospital.
* This investigation was supported, in part, by the Otto Baer Fund for Clinical Research and by a fund for the study of undernutrition in children, contributed jointly by the Elizabeth McCormick Memorial Foundation, Mrs. Francis Neilson, and Mrs. M. L. Rothschild.

The supply of milk for the days when specimens were taken was prepared at the beginning of the experiment. The required amount of breast milk was expressed from three wet-nurses and thoroughly mixed. When the milk was mixed and ready for use, a sample was removed for analysis, while the rest was preserved with formaldehyd in the proportion of 1:40,000. This was not sufficient preservative to cause any change in the taste of the milk or disturbance in digestion. The cow's milk used was pasteurized and modified by the addition of water and dextrimaltose. The mixture was made to approximate the composition of the breast milk for the same infant. This was likewise preserved with formaldehyd. The modification varied with the age and weight of the child, and was designed to assure a normal gain in weight.

Male infants were used exclusively because of the greater facility of collecting specimens. The child was placed on a hammock swung in a bassinet, and kept there for the duration of the experiment. None of the infants showed any signs of discomfort from their position in the hammock. They were weighed before they were placed on the frame and at the end of the time spent there. Urine was collected by means of a Schloss tube, and feces were collected in a pail placed under an opening in the canvas.

No results are reported where there was any loss in food intake either by refusal of the child to take the food or inability to retain it.

Twenty-four-hour specimens of urine were collected, measured, and then preserved with toluol. The feces were collected in an enamel pail and dried in the same pail over a steam bath. The weight was determined by difference, and the dry feces were scraped from the pail, ground, and further dried by placing over sulphuric acid in a vacuum desiccator. They were then preserved in an air-tight glass container. Methods of analysis and experimental data will appear in subsequent papers.

An attempt was made to determine the corresponding mineral content of the blood. For this purpose about 10 c.c. of blood was drawn from the superior longitudinal sinus, centrifuged immediately, and the salts were determined on the plasma. Difficulty was encountered in most cases, however. The reliable results obtained will be discussed in subsequent papers.

EXPERIMENTAL DATA

EXPERIMENT 1.—W. O., one of twin brothers, was a normal baby, 8 weeks and 6 days old, weighing 4.09 kg., when first placed on the metabolism frame. He was tested for four periods each lasting three days, alternating cow's and breast milk, but the first period was discarded because of the loss of a part of a specimen. One week was allowed for the change of diet between each two periods. He was apparently normal during the whole experiment, which covered a period of thirty-two days; during this time he gained 360 gm. The

modification of cow's milk during the third period consisted of whole milk, one half; boiled water, one-half, and 3.5 per cent. dextrimaltose.

EXPERIMENT 2.—E. M. admitted to hospital at the age of 5 months for the metabolic experiment, was normal in every respect, and weighed 7.34 kg. at this time. His first period on the frame was with whole milk, two-thirds; boiled water, one-third, and 3 per cent. dextrimaltose, receiving five 7 ounce (207 c.c.) feedings daily. During these three days he gained 120 gm. but during the period of change of diet he lost 150 gm. The second period, five days after the end of the first period, consisted of only two days on breast milk, during which time he gained 30 gm. However, he seemed to be in good health.

EXPERIMENT 3.—T. O., twin brother of W. O., was also a normal baby, smaller than his twin. He was 12 weeks and 6 days old, weighing 3.54 kg., when first put on the frame on a diet of breast milk, receiving six feedings of 4 ounces (118.4 c.c.) each. During this period he gained 60 gm. A month later he was on the frame again, receiving six 5 ounce (148 c.c.) feedings a day of a mixture of 17 ounces (503 c.c.) of whole milk, 12 ounces (355 c.c.) of boiled water, and 1 ounce (28.3 gm.) of dextrimaltose. During this period he lost 60 gm., otherwise he was quite well.

EXPERIMENT 4.—B. N., born in the hospital, was also normal. He was first put on the frame when 11 days old, weighing 3.24 kg., with seven 3 ounce (89 c.c.) feedings consisting of whole milk, one-half; boiled water, one-half, and 4 per cent. dextrimaltose. He gained 60 gm. during the three days. When a month old he was on the frame again with seven 3½ ounce (104 c.c.) feedings of breast milk each day. In this period he gained 112 gm. He was in good health throughout the experiment.

EXPERIMENT 5.—B. B., admitted to the hospital when four hours old because his mother was unable to take care of him, was a normal baby. He was observed for six periods, lasting three days each, three on cow's milk and three on breast milk. He gained in each breast milk period. In the first period on cow's milk at 5 weeks of age he neither gained nor lost. His greatest gain was at the age of 9 weeks on a diet of cow's milk. At this time he gained 142 gm. He was first put on the frame at the age of 5 weeks, weighing 3.82 kg., on a mixture of whole milk, one-half; boiled water, one-half, and 4 per cent. dextrimaltose, seven 4 ounce (118.4 c.c.) feedings. During the second period on cow's milk he received seven 4½ ounce (133.4 c.c.) feedings of a mixture of 18 ounces (532 c.c.) whole milk, 14 ounces (414 c.c.) boiled water, and 1 ounce (28.3 gm.) dextrimaltose. His third period on cow's milk came at the age of 27 weeks. He then received five 7½ ounce (222 c.c.) feedings of a mixture of whole milk, two-thirds; boiled water, one-third, and 4 per cent. dextrimaltose. His first period on breast milk was at the age of 6½ weeks, when he received seven 4 ounce (118.4 c.c.) feedings daily; during the second, at 11 weeks, he had seven 4½ ounce (133.4 c.c.) feedings; and during the third, at 4⅙ months, he had six 6 ounce (178 c.c.) feedings daily. He was a well nourished child and in good health during all the experimental periods.

CALCIUM METABOLISM[1]

The work reported in this paper was designed to compare the utilization of the calcium of breast milk with that of cow's milk by the same infant. Since little other work has been done on this particular problem, opportunity is lacking for comparison of our work with that of other

1. Metabolism Studies Reported by Chi Che Wang, Ph.D., and Augusta R. Felcher, A. B.

investigators. In the course of our experiments, however, so many points have come up on the general problem of calcium metabolism, where our findings vary considerably from those previously reported, that we have deemed it advisable to discuss the general question of calcium metabolism in infants fed on breast milk and cow's milk, as well as the calcium metabolism in the same infant fed on both breast and cow's milk.

REVIEW OF LITERATURE

Much work has been done on the subject of calcium metabolism, but the comparison was almost invariably made on different infants. The only literature that we were able to find on the calcium metabolism of the two kinds of milk by the same infant is the paper reported by Peiser.[2] His study was made on four infants, only two of whom were normal. His figures for the calcium utilization and calcium retention with both kinds of milk are rather low. His results, along with ours, are shown below.

Blauberg[3] and Hoobler[4] found a higher utilization of calcium from breast milk than from cow's milk. Their conclusions represent a comparison of different subjects. The latter author notes, however, that the calcium intake in cow's milk is about eight times as great as in breast milk, and that the actual amount retained and absorbed is about four times as great. He concludes that the calcium of breast milk is much better metabolized than that of cow's milk, and since a healthy nursing infant shows no deficiency of calcium, the amount that it receives is evidently the true measure of the calcium required. Calcium is eliminated almost entirely through the feces; only from 5 to 10 per cent. of the intake appearing in the urine. There is little variation in the amount of calcium eliminated in the urine of infants fed on breast and cow's milk; in the feces there is great variation. In the case of cow's milk feeding, calcium makes up from one-quarter to one-third of the dried feces. This author finds great individual difference in the amount of calcium absorbed, and a further difference in the ability to retain the calcium absorbed. Givens,[5] on the other hand, states that an increased

2. Peiser, A.: Beiträge zur Kenntnis des Stoffwechsels, besonders der Mineralien im Säuglingsalter, IV. Vergleichende Untersuchungen über den Stoffumsatz bei Ammenmilch und Eiweissmilch mit besonder Berücksichtizung des Schwefelhaushaltes, Jahrb. f. Kinderh. **81**:437, 1915.

3. Blauberg, M.: Experimentelle Beiträge zur Frage über den Mineralstoffwechsel beim künstlich enrährten Säugling, Ztschr. f. Biol. **40**:1, 1900; Ueber den Mineralstoffwechsel beim natürlich ernährten Säugling, Ztschr. f. Biol. **40**:36, 1900.

4. Hoobler, B. R.: The Rôle of Mineral Salts in the Metabolism of Infants. Am. J. Dis. Child. **2**:106 (Aug.) 1912.

5. Givens, M. H.: Calcium and Magnesium Metabolism in Man, J. Biol. Chem. **34**:119 (April) 1918.

intake of calcium in the form of milk gives rise to an increased urinary output of calcium. Calcium absorption bears no relation to the body weight, but is influenced by the diet and by the tissue reserves of the subject.

Hamilton [6] and Telfer,[7] like Hoobler, find that calcium is excreted mainly in the feces, the amount depending largely on the percentage of calcium in the diet. Hamilton worked with premature, breast-fed infants, and found that three-fourths of them had a low calcium retention during the first months of life; this may have been due to rachitis, as craniotabes appeared in the second month. Where the intake exceeded 0.200 gm. the calcium retention was sufficient, a lower intake resulted usually in insufficient retention. Telfer used cow's milk for his subjects, and noted that when the calcium intake was low diarrhea often ensued. When an excess of calcium was present in the diet, there was increased excretion in the feces and a slight rise in the urinary calcium, the latter denoting an increase in calcium absorption.

Rothberg [8] reports that calcium retention varies little, between from 14 to 26 per cent. of the calcium intake. In general, a large intake is followed by a large retention, and vice versa, but there is no definite relation. Wolff [9] noted that an increase in calcium intake caused an immediate change of the calcium balance from negative to positive.

Orgler,[10] in a monograph published in 1912, on the calcium metabolism of infants, included a comprehensive table of the work then published on this subject, and concluded therefrom that 0.130 gm. of calcium monoxid daily is the minimum of normal retention. Hamilton,[11] in his later work on premature infants, found only five out of twelve whose calcium retention attained this magnitude. He found also a certain correlation between calcium retention and the age and weight of the child. In infants under 3 months the retention is from 0.042 to 0.093 gm. daily, and in infants over 3 months it is from 0.127 to 0.181 gm. daily. There is wide individual variation, however.

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6. Hamilton, B.: The Calcium Metabolism of Premature Infants, Am. J. Dis. Child. **20**:316 (Oct.) 1920.

7. Telfer, S. V.: The Influence of Free Fatty Acids in the Intestinal Contents on the Excretion of Calcium and Phosphorus, Biochem. J. **15**:347, 1921; Studies on Calcium and Phosphorus Metabolism. The Excretion of Calcium and Phosphorus, Quart. J. Med. **16**:45 (Oct.) 1922.

8. Rothberg, O.: Ueber den Einfluss der organischen Nahrungskomponenten (Eiweiss, Fett, Kohlehydrate) auf den Kalkumsatz künstlich genährter Säuglinge, Jahrb. f. Kinderh. **66**:69, 1907.

9. Wolff, G.: Ueber den Kalk-und Phosphorsäurestoffwechsel des Säuglings bei knapper und reichlicher Ernährung mit Kuhmilch, Jahrb. f. Kinderh. **76**:180, 1912.

10. Orgler, A.: Ueber den Kalkstoffwechsel bei Rachitis, Monatschr. f. Kinderh. **10**:373, 1911.

11. Hamilton, B.: The Calcium and Phosphorus Metabolism of Prematurely Born Infants, Acta Pediat. **2**:1, 1922.

METHOD

The excretions were prepared as described above. About 2½ gm. of the finely powdered feces was accurately weighed into a silica crucible, 2 c.c. of concentrated sulphuric acid was added, and the whole was put in the oven to ash. The ash was dissolved in 50 c.c. of 10 per cent. hydrochloric acid, made up to 100 c.c. with distilled water, and filtered through a dry, ashless filter. The calcium determinations were then made according to McCrudden's [12] method. For the calcium determination in urine and milk, also, McCrudden's method was carefully followed. Two hundred cubic centimeters of urine was used for each determination. In the determination of milk, about 10 gm. was accurately weighed into a silica crucible, 1 c.c. of concentrated sulphuric acid was added, and the mixture allowed to ash. The ash was dissolved in 25 c.c. of 10 per cent. hydrochloric acid, made up to 100 c.c. with distilled water and filtered in the same way as the feces. From that point on, the same author's method as for feces was used. In the urine the gravimetric method was employed, but for the calcium determination in feces and in milk the calcium was titrated with potassium permanganate.

All determinations were made in duplicate, and the results given below are the average of the two.

Since Holt [13] and Holt and Fales [14] reported a relationship between calcium metabolism and fat intake, the fat in the milk was determined by the Babcock method in these experiments. These authors report that calcium absorption is aided by a relatively high fat content, giving as the minimum fat requirement from 3 to 4 gm. per kilogram. They also state that a desirable amount of calcium in the diet is represented by the ratio of from 0.03 to 0.05 gm. of calcium monoxid to 1 gm. of fat. Our fat intake per kilogram was never below the minimum figure here given, whereas the ratio of fat to calcium monoxid was slightly lower in breast milk and somewhat higher in cow's milk. However, the slight variation in this ratio did not seem to have any effect on the calcium metabolism; in fact, the case of highest calcium utilization and retention, which occurred with breast milk, showed a fat calcium monoxid ratio of slightly less than 1 : 0.003, and the case where the ratio was high,

12. McCrudden, F. H.: The Quantitative Separation of Calcium and Magnesium in the Presence of Phosphates and Small Amounts of Iron Devised Especially for the Analysis of Foods, Urine, and Feces, J. Biol. Chem. **7**:83, 1911; The Determination of Calcium in the Presence of Magnesium and Phosphates; the Determination of Calcium in Urine, J. Biol. Chem. **10**:187, 1911.

13. Holt, L. E.; Courtney, A. M., and Fales, H. L.: Calcium Metabolism in Infants and Young Children and Relation of Calcium to Fat Excretion in Stools, Am. J. Dis. Child. **19**:97 (Feb.), 201 (March) 1920.

14. Holt, L. E., and Fales, H. L.: Calcium Absorption in Children on a Diet Low in Fat, Am. J. Dis. Child. **25**:247 (March) 1923.

1 : 0.09, showed a percentage calcium utilization and retention of 52.0 and 51.5 respectively, which are next to the maximum figures for cow's milk.

CONCLUSIONS

Table 1 shows that with the exception of one period in Case 1, the daily value of calcium excretion in the feces varies greatly. The maximum variation occurs in the case of E. M. where, of two successive days, 0.4513 gm. of calcium monoxid was excreted on the first day; this was 2.6 times as great as the amount on the second day, which showed 0.1730 gm. The nonconcordant results may be owing chiefly to the failure always to empty the bowels completely at the end of every twenty-four hours. It is clear, then, that for metabolic investigations the study of individual twenty-four-hour specimens, or one single twenty-four-hour specimen, has little or no value. However, as Table 2 shows, the average daily output of three-day periods gives results which bear distinct differences brought about by a change of diet. Although our analyses were made on twenty-four-hour specimens, our discussion will be based on the average of three consecutive day periods.

With the urine the daily variation is not so marked. Since the amount of calcium in urine is so small—only a few milligrams in a twenty-four-hour specimen—the difference that does exist may be in part attributed to experimental error.

Difference in the Quantity of Calcium Excretion in Feces and Urine Brought About by the Change of Milk.—Table 2, which gives the average daily value per three-day period, shows that a change of milk brought about a distinct change in the quantity of calcium excreted in the feces in every child. The quantity of calcium excreted is invariably greater when the infant is on a diet of cow's milk. The difference of calcium as calcium monoxid in the excretions of the same child ranged from 0.0726 to 0.7829 gm. with an average of 0.4639, which is in agreement with that reported by Peiser,[2] who in his investigation tried two five-day periods on two normal patients. One period on each child was tested with breast milk and the other with cow's. Tables 3 and 4 show that in both cases the change from breast milk to cow's milk brought a large increase in the excretion of calcium in the feces. With breast milk the calcium in the feces in one case was 0.287 and in the other 0.211 gm. When the diet was changed to cow's milk, the calcium monoxid excreted was 0.894 gm. in the first case and 0.591 gm. in the second, which gives an increase of 0.607 and 0.380 gm. respectively, with an average of 0.493 gm.

In the case of the last of our periods tried on B. B. (Table 2), the first and last were with cow's milk and the second and third with breast milk. We see that the quantity of calcium monoxid excreted in the

TABLE 1.—*Daily Calcium Metabolism in Healthy Infants Fed on Breast Milk and Cow's Milk*

Name	Kind of Milk	Date	CaO Intake		CaO Output				CaO Utilization			CaO Retention		
			Per 24 Hours, Gm.	Per Kg. per 24 Hours, Gm.	Feces per 24 Hours, Gm.	Urine per 24 Hours, Gm.	Total per 24 Hours, Gm.	Total per Kg. per 24 Hours, Gm.	Per 24 Hours, Gm	Per Kg. per 24 Hours, Gm.	Per Cent. of Intake	Per 24 Hours, Gm.	Per Kg. per 24 Hours, Gm.	Per Cent. of Intake
W. O	Breast.....	11/26/21	0.6452	0.157	0.2678	0.0171	0.2849	0.069	0.3774	0.092	58.5	0.3603	0.088	55.8
		11/27/21	0.6452	0.156	0.2080	0.0074	0.2754	0.066	0.3772	0.091	58.5	0.3698	0.090	57.3
		11/28/21	0.6452	0.155	0.2687	0.0178	0.2865	0.069	0.3765	0.090	59.2	0.3587	0.086	55.6
	Cow's.....	12/ 7/21	1.0932	0.250	0.7357	0.0109	0.7484	0.171	0.3575	0.081	32.5	0.3448	0.079	31.5
		12/ 8/21	1.0932	0.248	0.5041	0.0112	0.5153	0.117	0.5891	0.134	53.9	0.5779	0.131	52.9
		12/ 9/21	1.0932	0.249	0.6356	0.0213	0.6569	0.149	0.4576	0.104	41.9	0.4363	0.100	39.9
	Breast.....	12/16/21	0.6285	0.140	0.2796	0.0174	0.2970	0.067	0.3489	0.078	55.5	0.3315	0.073	52.7
		12/17/21	0.6285	0.141	0.1952	0.0181	0.2133	0.047	0.4333	0.097	68.9	0.4152	0.094	66.0
		12/18/21	0.6285	0.141	0.2445	0.0106	0.2551	0.057	0.3840	0.086	61.1	0.3734	0.084	59.4
E. M	Cow's.....	11/26/21	1.5700	0.212	1.0400	0.0083	1.0483	0.142	0.0530	0.071	33.8	0.5217	0.070	33.2
		11/27/21	2.6160	0.351	1.4510	0.0162	1.4672	0.196	0.1165	0.156	44.6	1.1488	0.155	43.9
		11/28/21	2.6550	0.356	0.7941	0.0105	0.8046	0.108	0.1861	0.249	70.1	1.8504	0.248	69.7
	Breast.....	12/ 3/21	0.8861	0.121	0.4513	0.0129	0.4642	0.063	0.4348	0.059	49.1	0.4219	0.058	47.6
		12/ 4/21	0.8982	0.122	0.1730	0.0141	0.1872	0.025	0.7252	0.098	80.7	0.7111	0.097	79.1
T. O.	Breast.....	12/13/21	0.5235	0.148	0.0930	0.0093	0.1023	0.028	0.4305	0.121	82.2	0.4212	0.119	80.5
		12/14/21	0.5235	0.148	0.0930	0.0093	0.1023	0.028	0.4305	0.121	82.2	0.4212	0.119	80.5
		12/15/21	0.5235	0.145	0.0902	0.0252	0.1154	0.032	0.4333	0.120	83.6	0.4081	0.113	77.9
	Cow's.....	1/14/22	1.4630	0.360	0.6745	0.0194	0.6859	0.169	0.7885	0.194	53.9	0.7721	0.191	53.1
		1/15/22	1.4630	0.360	0.6745	0.0194	0.6859	0.169	0.7885	0.194	53.9	0.7721	0.191	53.1
		1/16/22	1.4630	0.367	0.7308	0.0150	0.7458	0.186	0.7322	0.183	50.1	0.7172	0.181	49.0
B. N.	Cow's.....	3/ 9/22	0.6704	0.269	0.5105	0.0172	0.5277	0.163	0.1569	0.049	23.9	0.1427	0.106	21.3
		3/10/22	0.6704	0.269	0.5157	0.0222	0.5379	0.166	0.1547	0.048	23.1	0.1305	0.103	19.4
		3/11/22	0.6704	0.263	0.2219	0.0183	0.2402	0.073	0.4485	0.136	66.9	0.4302	0.190	64.1
	Breast.....	3/30/22	0.7821	0.217	0.3049	0.0055	0.3104	0.086	0.4772	0.132	61.0	0.4717	0.131	60.3
		3/31/22	0.7821	0.217	0.3049	0.0055	0.3104	0.086	0.4772	0.132	61.0	0.4717	0.131	60.3
		4/ 1/22	0.7821	0.217	0.4204	0.0131	0.4335	0.120	0.3617	0.099	46.3	0.3486	0.097	44.5
B. B.	Cow's.....	2/25/22	1.0230	0.267	0.6840	0.0178	0.7017	0.184	0.3390	0.089	33.1	0.3213	0.083	31.4
		2/26/22	1.0230	0.267	0.6840	0.0178	0.7017	0.184	0.3390	0.089	33.1	0.3213	0.083	31.4
		2/27/22	1.0230	0.267	0.6241	0.0175	0.6416	0.160	0.3989	0.104	39.0	0.3814	0.107	37.2
	Breast.....	3/ 8/22	0.7196	0.180	0.1867	0.0141	0.2008	0.050	0.5329	0.133	74.0	0.5188	0.130	72.0
		3/ 9/22	0.7196	0.180	0.3056	0.0164	0.3220	0.081	0.4140	0.104	57.5	0.3976	0.099	55.2
		3/10/22	0.7196	0.180	0.3111	0.0160	0.3271	0.082	0.4085	0.102	56.8	0.3925	0.098	54.6
	Cow's.....	3/29/22	1.4680	0.330	0.5857	0.0158	0.6015	0.135	0.8823	0.198	60.1	0.8665	0.195	59.0
		3/30/22	1.4680	0.330	0.8690	0.0186	0.8876	0.199	0.5990	0.135	40.8	0.5804	0.131	39.5
		3/31/22	1.4680	0.330	0.8690	0.0186	0.8876	0.199	0.5990	0.135	40.8	0.5804	0.131	39.5
	Breast.....	4/11/22	0.6446	0.138	0.3035	0.0168	0.3203	0.069	0.3411	0.073	52.9	0.3243	0.069	50.3
		4/12/22	0.7147	0.153	0.3824	0.0137	0.3961	0.086	0.5823	0.071	46.5	0.3186	0.067	44.5
		4/13/22	0.7147	0.153	0.2370	0.0105	0.2475	0.054	0.4777	0.102	66.8	0.4672	0.099	65.3
	Breast.....	5/23/22	0.7008	0.138	0.3387	0.0147	0.3534	0.064	0.4221	0.076	55.5	0.4074	0.074	53.5
		5/24/22	0.8851	0.155	0.2008	0.0248	0.2256	0.040	0.6543	0.119	76.5	0.6295	0.115	73.6
		5/25/22	0.8024	0.146	0.3924	0.0199	0.4123	0.075	0.4100	0.074	51.1	0.3901	0.071	48.6
	Cow's.....	7/10/22	1.9050	0.279	0.4835	0.0287	0.5122	0.075	1.4195	0.209	74.6	1.3908	0.204	73.0
		7/11/22	1.9030	0.279	0.5674	0.0267	0.5941	0.087	1.3356	0.206	70.2	1.3089	0.192	68.7
		7/12/22	1.9030	0.279	0.9504	0.0222	0.9726	0.142	0.9526	0.140	50.1	0.9304	0.137	48.8

TABLE 2.—*Average Daily Calcium Metabolism of Healthy Infants Fed on Breast Milk and Cow's Milk*

Name	Age in Mos.	Body Weight, Kg.	Kind of Milk	Fat in Milk, per Cent.	CaO Intake		CaO Output				CaO Utilization			CaO Retention		
					Per 24 Hrs., Gm.	Per Kg. per 24 Hrs., Gm.	Feces per 24 Hrs., Gm.	Urine per 24 Hrs., Gm.	Total per 24 Hrs., Gm.	Per Kg. per 24 Hrs., Gm.	Per 24 Hrs., Gm.	Per Kg. per 24 Hrs., Gm.	Per Cent. of Intake	Per 24 Hrs., Gm.	Per Kg. per 24 Hrs., Gm.	Per Cent. of Intake
W. O.	2.6	4.13	Breast	4.0	0.6452	0.156	0.2682	0.0141	0.2822	0.068	0.3770	0.091	58.4	0.3630	0.088	56.2
	3.0	4.39	Cow's	...	1.0932	0.248	0.6257	0.0144	0.6401	0.146	0.4681	0.106	42.8	0.4530	0.102	41.4
	3.3	4.46	Breast	4.4	0.6285	0.141	0.2397	0.0154	0.2551	0.057	0.3887	0.087	61.9	0.3734	0.084	59.4
E. M.	5.5	7.43	Cow's	2.2	2.2800	0.307	1.0960	0.0116	1.1066	0.149	1.1850	0.161	52.0	1.1736	0.159	51.5
	5.7	7.23	Breast	3.8	0.8921	0.121	0.3121	0.0130	0.3251	0.044	0.5800	0.079	65.0	0.5665	0.077	63.6
T. O.	3.2	3.57	Breast	4.0	0.5235	0.147	0.0921	0.0146	0.1067	0.029	0.4314	0.121	82.4	0.4168	0.117	79.6
	4.3	4.03	Cow's	2.2	1.4630	0.363	0.6932	0.0179	0.7059	0.174	0.7697	0.190	52.6	0.7538	0.188	51.7
B. N.	0.4	3.26	Cow's	2.1	0.6704	0.206	0.4160	0.0193	0.4353	0.133	0.2545	0.078	37.9	0.2344	0.073	35.1
	1.4	3.61	Breast	3.6	0.7821	0.217	0.3434	0.0080	0.3514	0.097	0.4387	0.121	56.9	0.4323	0.119	55.1
B. B.	1.3	3.82	Cow's	2.0	1.0230	0.267	0.6640	0.0177	0.6816	0.178	0.3590	0.094	35.1	0.5120	0.089	33.4
	1.6	3.99	Breast	4.2	0.7196	0.180	0.2678	0.0155	0.2833	0.071	0.4518	0.113	62.8	0.4363	0.109	60.6
	2.1	4.44	Cow's	2.2	1.4680	0.330	0.7746	0.0177	0.7922	0.178	0.6934	0.156	47.2	0.6758	0.152	46.0
	2.4	4.66	Breast	3.3	0.6913	0.148	0.3076	0.0137	0.3213	0.070	0.3837	0.082	55.5	0.3700	0.078	53.5
	4.6	5.50	Breast	3.3	0.8161	0.146	0.3106	0.0198	0.3304	0.060	0.4954	0.090	61.5	0.4756	0.086	59.0
	6.1	6.82	Cow's	2.0	1.9030	0.279	0.6671	0.0259	0.6930	0.101	1.2359	0.183	65.0	1.8150	0.178	63.5

feces of the two breast milk periods, although six weeks apart, varied only slightly, 0.0030 gm., and was proportional to the age of the child. The amount excreted with cow's milk during the period immediately preceding and the one immediately following the two breast milk periods is more than twice as much as that excreted with breast milk. The difference of calcium excreted between the first and second periods is 0.4670 gm., and that between the third and fourth is 0.3565 gm.

The calcium excretion through the feces in all our cases ranges from 0.0921 gm. to 0.3434 gm., with an average of 0.2677 gm. with breast milk. Fifty per cent. of our cases give higher values than the maximum figures reported by previous investigators. Their values range from 0.0312 to 0.287 (Table 3). With cow's milk our figures ran from 0.4160 gm. to 1.095 gm., with an average of 0.7051 gm., as against their range of 0.5600 to 2.2687. The discrepancy between our results and those of other investigators in the case of breast milk is probably because of the difference in the amount of calcium intake. Our intake per kilogram varied between 0.141 gm. and 0.217 gm., whereas other investigators report a per kilogram intake of 0.047 gm. to 0.088 gm. Hamilton [11] suggests that a rough average calcium intake should be 0.200 to 0.400 gm. daily. Our calcium intake is lower than this, but even so, it is from two to four times higher than that reported in previous work. It is therefore possible that the infants in the experiments reported by previous investigators were not getting sufficient food, at least during the experimental periods, and the amount excreted might thus be the minimum calcium output of each subject. The investigation of this point is now in progress.

On the other hand, our figures for the calcium output in the feces with cow's milk are lower than theirs. This may possibly be owing to the difference in methods of modification. Peiser,[2] for instance, used evaporated milk, and Blauberg [3] used sterilized milk. In all cases where formulas are given, the same formula is used for children of different ages. In our experiments, pasteurized milk was used which was modified with water and dextrimaltose to approximate the individual child's breast milk requirements. Individual formulas are given above. So far as the calcium intake is concerned, our figures run between 0.6704 and 2.280 gm. with an average of 1.4144 gm. as compared with the above mentioned authors, whose intake is from 0.654 to 2.0536 gm.

The difference brought about in the calcium excretion in the urine with a change in diet is slight and inconsistent. Out of nine changes, four were from breast to cow's milk, and five from cow's to breast milk. In the change from breast to cow's milk, the maximum difference was an increase of 6 mg. with cow's milk; in the change from cow's to breast milk, in three cases there was a decrease in the calcium excretion

TABLE 3.—*Calcium Metabolism of Healthy Infants Fed on Breast Milk*

Author	Subject	Duration of Period, Days	Age in Mos.	Body Weight, Kg.	CaO Intake		CaO Output			CaO Utilization			CaO Retention		
					Per 24 Hrs., Gm.	Per Kg. per 24 Hrs., Gm.	Feces per 24 Hrs., Gm.	Urine per 24 Hrs., Gm.	Total per 24 Hrs., Gm.	Per 24 Hrs., Gm.	Per Kg. per 24 Hrs., Gm.	Per Cent. of Intake	Per 24 Hrs., Gm.	Per Kg. per 24 Hrs., Gm.	Per Cent. of Intake
Peiser [2]	1	5	3.0	3.800	0.3350	0.088	0.2870	0.0360	0.3230	0.0480	0.0130	14.30	0.0120	0.0030	3.58
	2	...	1.5	3.720	0.2790	0.075	0.2110	0.0210	0.2320	0.0680	0.0180	24.40	0.0480	0.0130	17.07
Tobler-Noll: Monatschr. f Kinderh. **9**: 210, 1910	...	6	2.5	4.040	0.2390	0.059	0.1485	0.0372	0.1857	0.0905	0.0220	37.80	0.0530	0.0133	22.30
Lindberg [18]	1	..	2.5	4.285	0.2572	0.060	0.1827	0.0183	0.2010	0.0745	0.0173	28.90	0.0562	0.0130	21.85
	1	...	...	4.370	0.2615	0.051	0.1748	0.0228	0.1976	0.0867	0.0198	33.10	0.0639	0.0150	24.44
	1	...	...	4.370	0.2397	0.055	0.1805	0.0131	0.2026	0.0502	0.0115	29.40	0.0371	0.0090	11.30
	1	...	...	4.370	0.2089	0.048	0.2201	0.0220	0.2421	—0.0112	—0.0025	.....	—0.0332	—0.0080	.....
Blauberg [3]	...	6	5.0	.....	0.2720	.....	0.0660	0.0310	0.0970	0.2060	.....	75.80	0.1750	.....	60.62
Michel-Perrett [15]	...	3	3.0	4.725	0.3770	0.080	0.1980	0.0300	0.2280	0.1790	0.0370	47.49	0.1490	0.0320	39.52
Michel [19]	...	3	0.17	3.730	0.2520	0.068	0.0312	0.0124	0.0436	0.2208	0.0590	87.50	0.2090	0.0560	82.80
		4	0.17	2.680	0.2317	0.086	0.0951	0.0076	0.1027	0.1367	0.0510	58.70	0.1290	0.0480	55.60
		6	0.23	3.500	0.2965	0.085	0.0950	0.0076	0.1026	0.2015	0.0570	68.00	0.1940	0.0550	65.50
		3	0.37	4.400	0.3010	0.068	0.0860	0.0147	0.1007	0.2150	0.0490	71.30	0.2000	0.0460	66.70
Schabad [16]	..	3	3.75	7.685	0.3636	0.047	0.1640	0.0186	0.1826	0.1996	0.0530	54.89	0.1810	0.0490	49.79

TABLE 4.—*Calcium Metabolism of Healthy Infants Fed on Cow's Milk (Modified)*

Author	Subject	Duration of Period, Days	Age in Mos.	Body Weight, Kg.	CaO Intake		CaO Output			CaO Utilization			CaO Retention		
					Per 24 Hrs., Gm.	Per Kg. per 24 Hrs., Gm.	Feces per 24 Hrs., Gm.	Urine per 24 Hrs., Gm.	Total per 24 Hrs., Gm.	Per 24 Hrs., Gm.	Per Kg. per 24 Hrs., Gm.	Per Cent. of Intake	Per 24 Hrs., Gm.	Per Kg. per 24 Hrs., Gm.	Per Cent. of Intake
Peiser [2]	1	5	3.0	3.80	0.8740	0.230	0.8940	0.0500	0.9440	—0.0150	—0.004	.....	—0.0700	—0.019	.....
	2	5	1.5	3.70	0.7280	0.197	0.5910	0.0570	0.6480	0.1370	0.037	18.80	0.0800	0.022	11.01
Blauberg [3]	...	4	..	....	0.7520	.....	0.5840	0.0140	0.5980	0.1680	.....	22.36	0.1540	.....	20.48
Telfer [7]	1	8	15.0	8.30	0.8200	0.099	0.6700	.. ...	.....	0.1500	0.018	18.30	.....	.....	.....
	2	...	8.0	6.50	0.8200	0.126	0.6800	0.0020	0.6820	0.1400	0.021	17.07	0.1380	0.021	16.08
	3	...	9.0	9.40	0.8000	0.085	0.5600	.....	.....	0.2400	0.025	30.00	.....	.....	.....
	1	...	6.0	6.45	0.8100	0.126	1.0000	0.0160	0.0160	—0.1900	—0.029	.....	—0.2060	—0.032	.....
Cronheim and Müller [17]	1	3	4.5	4.95	0.6540	0.132	0.8420	0.0150	0.8570	—0.1880	—0.038	.....	—0.2030	—0.041	.....
	2	4	6.0	6.50	1.2750	0.196	1.1910	0.0118	1.2028	0.0840	0.013	6.58	0.0722	0.011	5.74
	3	4	4.0	6.90	1.3530	0.196	0.9180	0.0170	0.9350	0.4350	0.063	32.13	0.4180	0.060	30.87
	4	4	4.0	3.84	0.8660	0.226	0.6820	0.0108	0.6928	0.1840	0.048	21.28	0.1732	0.045	20.03
	5	4	6.0	7.80	1.4130	0.181	1.3520	0.0438	1.3958	0.0610	0.008	4.30	0.0170	0.002	1.20
Hoobler [4]	...	...	...	....	2.0536	.....	2.2687	0.0301	2.2988	—0.2151	.....	.....	—0.2452	.....	.....

with breast milk and in two there was an increase; the maximum increase was 2 mg. and the maximum decrease was 11 mg. With breast milk the calcium excretion through the urine in all the children runs between 0.008 gm. and 0.0198 gm., with an average of 0.0143 gm.; while with cow's milk it lies between 0.0116 gm. and 0.0259 gm., with an average of 0.0178 gm. We see, therefore, that with cow's milk there is a slight increase in the average value. In the two cases reported by Peiser [2] the calcium excretion in urine with breast milk was 0.036 gm. in the first case and 0.021 gm. in the second; with cow's milk it was 0.050 and 0.057 gm., respectively. His difference is therefore 0.014 gm. in the first child and 0.036 gm. in the second, with an average of 0.025 gm. This is more than twice as high as the maximum difference in our infants. The calcium excretion through the urine in all the cases reported in Table 3 lies between 0.008 and 0.037 gm. with breast milk, and from 0.002 to 0.057 gm. with cow's milk. Because of the very small amounts of calcium involved in the urinary excretion and the possibility of experimental error, it is difficult to say whether there is any significance in the different results.

The Effect of the Change of Milk on the Utilization and Retention of Calcium.—This is well marked. Aside from B.N., the actual quantity of calcium utilized is greater with cow's than with breast milk. With the former the calcium utilization per twenty-four hours runs from 0.2545 to 1.2359 gm., with an average of 0.7094 gm., while with the latter it varies between 0.3770 and 0.5800 gm., with an average of 0.4433 gm. With breast milk the calcium utilization per twenty-four hours reported by previous investigators and summarized in Tables 3 and 4 lies between —0.0112 and +0.2208 gm., and with cow's milk it is from —0.1880 to +0.4350. Of the fourteen periods on breast milk and thirteen periods on cow's milk tried by these authors, one period gave a negative balance with the former and four periods with the latter. In our cases we had no negative balance with either kind of milk. These figures show that the quantity utilized with both cow's and breast milk is much greater in our work than in the work reported by the above authors. Our minimum value is greater than the maximum reported in Table 3 with breast milk, and with the exception of one case the same holds true in Table 4 for cow's milk. In agreement with their figures, however, the actual quantity of calcium utilized is greater with cow's than with breast milk, the average figures being 0.7094 as against 0.4433 gm.

The percentage utilization of calcium is almost invariably greater with breast milk. The only period which showed a greater percentage of utilization with cow's milk is the last period of the work on B.B. This difference is probably due to difference in age, which will be dis-

cussed later. The percentage utilization with breast milk is between 55.50 and 82.40 with an average of 63.04; with cow's milk it is from 35.09 to 64.95 with an average of 47.51. With the exception of the figures showing a negative balance, the other investigators report percentages ranging from 11.80 to 87.50 for breast milk. For cow's milk their values are from 4.30 to 32.13. In all cases except those of Blauberg,[3] Michel,[15] and Schabad,[16] the percentage utilization of breast milk is less than our minimum figure. The difference in the case of cow's milk is even greater. The discrepancy may be accounted for by the criticism of Schabad[16] and Hamilton,[6] who have pointed out that the work of Blauberg[3] and Cronheim and Müller[17] may be criticized on the ground of insufficient intake of milk or insufficient calcium content of the milk fed. Hamilton criticizes Schabad on the same point.

Since the amount of calcium excreted in the urine is rather insignificant and fairly constant, the effect of a changed milk diet on the retention of calcium is similar to that on the utilization. The actual amount retained with cow's milk is greater in every case except in that of B.N.

In breast milk the actual amount of calcium retained ranges from 0.3630 to 0.5665 gm. per twenty-four hours, an average of 0.4524 gm., and a per kilogram range of from 0.077 to 0.119 gm. The range with cow's milk is from 0.2344 to 1.815 gm. per twenty-four hours, an average of 0.8025 gm., and a per kilogram range of from 0.073 to 0.188 gm. This is a much greater range for cow's milk in both total and relative amounts of calcium retained. Aside from the negative results of Lindberg,[18] the range for breast milk obtained by other investigators is from 0.003 to 0.2090 gm. per twenty-four hours, with a per kilogram range of 0.0019 to 0.0560 gm. With eleven cases of cow's milk feeding reported by other investigators four cases give a negative calcium balance. The rest range from 0.0170 to 0.4180 gm. retention per twenty-four hours, with a per kilogram range of from 0.002 to 0.060 gm. The figures show clearly that our work is much more uniform, showing a per kilogram variation in range of from one and a half times the minimum

15. Michel, C.: Recherches, sur la nutrition normale, du nouveau-né echanges nutritifs azotés et salins, L'obstétrique, **1**:140, 1896.

16. Schabad, J. A.: Zur Bedeutung des Kalkes in der Pathologie der Rachitis, Arch. f. Kinderh. **54**:83, 1910.

17. Cronheim, W., and Müller, E.: Versuche über den Stoff—und Kraftwechsel des Säuglings mit besonderer Berücksichtung des organisch gebundenen Phosphors, Ztschr. f. diätet. u. physik. Therap. **6**:25, 1903; Untersuchungen über den Einfluss der Sterilisation der Milch auf den Stoffwechsel des Säuglings unter besonderer Berücksichtung der Knochenbildung, Jahrb. f. Kinderh. **57**:45, 1903; Stoffwechselversuche an gesunden und rachitischen Kindern mit besonderer Berücksichting des Mineralstoffwechsels, Biochem. Ztschr. **9**:76, 1908.

18. Lindberg, G.: Ueber den Stoffwechsel des gesunden, natürlich ernährten Säuglings und dessen Beeinflussung durch Frauenmilchfett, Ztschr. f. Kinderh. **16**:90, 1917.

value in case of breast milk to two and a half times for cow's milk, as against their variation of more than fifty times for breast milk and thirty times for cow's milk. This holds true not only by comparison with all cases, but also by comparison with the work of individual investigators. For example, Lindberg [18] worked with the same infant fed with breast milk for four periods, and found a variation of —0.008 to 0.015 gm. per kilogram, or three times the minimum value. The variation of the work reported by Cronheim and Müller [17] with cow's milk is far greater. The retention per kilogram ranged from —0.0041 to 0.4180 gm., which is about 103 times the minimum. On the other hand, the work of Michel [19] is more consistent, and he reports a relative range even smaller than ours. His calcium retention per kilogram per twenty-four hours for breast milk is from 0.046 to 0.056 gm., which is less than one and a quarter times the minimum.

TABLE 5.—*Relation of Age to Calcium Metabolism, Breast Milk*

Name	Age in Months	CaO Utilization		CaO Retention	
		Gm. per 24 Hours	Per Cent. of Intake	Gm. per 24 Hours	Per Cent. of Intake
B. N.	1.4	0.4387	56.9	0.4323	55.1
B. B.	1.6	0.4518	62.8	0.4363	60.6
B. B.	2.1	0.3887	55.5	0.3700	53.4
W. O.	2.6	0.3770	58.4	0.3630	56.2
T. O.	3.2	0.4314	82.4	0.4168	79.6
W. O.	3.3	0.3887	61.9	0.3734	59.4
B. B.	4.6	0.4954	61.5	0.4756	59.0
E. M.	5.7	0.5800	65.0	0.5665	63.6

The percentage retention of breast milk calcium in our cases is from 53.5 to 79.6; that of Michel runs from 49.79 to 82.80, while the range of all other investigators reported is from 1.11 to 82.80, disregarding negative values. Excluding Michel's results, there was only one case which attained our minimum value. In the case of cow's milk, our range is from 33.4 to 63.5 per cent.; that of other investigators, aside from the four cases of negative balance, is from 1.2 to 30.87 per cent. Thus the percentage retention of calcium in cow's milk is far greater in our work than in any of the experiments previously reported. With such a discrepancy in results it must be concluded that the methods of experimentation used are not comparable. The difference in the modification of cow's milk used has already been mentioned.

Effect of Age on Calcium Metabolism.—An examination of Table 5 shows that the calcium utilization and calcium retention of breast milk are independent of the age of the infant. Thus the percentage utilization in children from 1.4 months to 5.7 months varies within only a

19. Michel, C., and Perret, M.: Étude des échanges nutritif azotés et mineraux chez un nourrisson, Bull. Soc. d'obstet. de Paris **2**:98, 1899.

10 per cent. range, with one exceptional case; the percentage retention varies directly with the percentage utilization, also within a 10 per cent. range. It is interesting to note, in the case of B.B., that the utilization and retention are greater at the age of 1.6 months than in either of the later periods. On the other hand, the calcium metabolism of cow's milk (Table 6) shows a distinct increase with the age of the child. Here, in infants from 0.4 to 6.1 months, there is a difference of 27.0 per cent. in utilization and 28.4 per cent. in retention, the higher figures occurring in the older children. Again referring to the case of B.B., we find that here the increase in both utilization and retention is almost proportional to the increase in the age of the child. When this infant was 1.3 months old he showed a calcium utilization of 35.1 per cent. and retention 33.4 per cent.; at 2.4 months the corresponding figures were 47.2 per cent. and 46.0 per cent.; and at 6.1 months, 65.0 per

TABLE 6.—*Relation of Age to Calcium Metabolism, Cow's Milk*

Name	Age in Months	CaO Utilization		CaO Retention	
		Gm. per 24 Hours	Per Cent. of Intake	Gm. per 24 Hours	Per Cent. of Intake
B. N.	0.4	0.2545	37.9	0.2344	35.1
B. B.	1.3	0.3590	35.1	0.5120	33.4
B. B.	2.4	0.6964	47.2	0.6758	46.0
W. O.	3.0	0.4681	42.8	0.4530	41.4
T. O.	4.3	0.7697	52.6	0.7538	51.7
E. M.	5.5	1.1850	52.0	1.1736	51.5
B. B.	6.1	1.2359	64.9	1.8150	63.5

cent. and 63.5 per cent. The percentage utilization of calcium in cow's milk does not reach the average figure of that of breast milk until the child has attained the age of 6 months. Because of the higher calcium content of cow's milk, the actual amount of calcium utilized by the child of 6 months or older is much higher when he is fed on cow's milk than when his diet consists of breast milk. In this connection there is the possibility that a child of 4 months or more does not receive sufficient calcium from a diet of breast milk to secure a maximum gain in weight unless it is supplemented from some other source. For instance, B.B., up to the age of 2.1 months, showed an increase in the calcium metabolism on both breast and cow's milk. This increase continued in the case of cow's milk, but not with breast milk. At the age of 2.1 months his actual utilization and retention of calcium was higher with cow's milk than with breast milk two and a half months later. At 6.1 months the figures for cow's milk are two and a half times the highest figures for breast milk, which occurred at the age of 4.6 months. Hamilton,[11] working with premature infants, also found a correlation between age and calcium metabolism.

SUMMARY

1. Owing to the failure completely to evacuate the bowels every twenty-four hours, accurate determinations can be secured only from average values of at least a three day period.

2. A change from breast milk to cow's milk, or vice versa, was invariably accompanied by a change in the quantity of calcium excreted in the feces; the actual quantity excreted was always greater on a diet of cow's milk. The difference in the calcium excretions of the same child ranged from 0.0726 to 0.7829 gm., with an average of 0.4364 gm. The difference in the calcium excretion in the urine brought on by a change in diet is slight and inconsistent.

3. Calcium absorption and retention run closely parallel, since the variation in the urinary calcium output is slight and of little significance.

4. The actual quantity of calcium absorbed and retained is greater for cow's milk than for breast milk, but the percentage utilization and retention is greater for breast milk, except with the older children. With cow's milk, the average utilization is 0.7094 gm. per twenty-four hours, and with breast milk 0.4433 gm. The percentage utilization of cow's milk is 47.5 and of breast milk 63.0. The figures for calcium retention show an average of 0.8025 gm. per twenty-four hours for cow's milk and 0.4524 gm. for breast milk, or a percentage retention in the first case of 46.1 and in the second 60.9.

5. The calcium metabolism of breast milk is independent of the age of the child, but that of cow's milk shows a distinct increase with the age of the child, both in individual cases and in the group of subjects. The percentage utilization and retention of calcium of breast milk in infants from 1.4 months to 5.7 months falls within a range of 10 per cent. In case of cow's milk with children from 0.4 months to 6.1 months, there is a range of 27.0 per cent. in utilization and 28.4 per cent. in retention, the higher figures occurring in case of the older children.

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20. Tobbler, L., and Noll, F.: Zur Kenntnis des Mineralstoffwechsels beim gesunden Brustkind, Monatschr. f. Kinderh. **9**:210, 1910.

ANEMIA IN THE NEW-BORN *

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Anemia of early infancy is of comparatively frequent occurrence, whereas anemia in the new-born is a rare event. The new-born among those babies destined from antenatal causes to become anemic after the lapse of several weeks, or months, almost always manifest at the time of birth and during the early weeks of life the red blood count and hemoglobin of the normal, healthy new-born. This fact is shown by the studies of Lichtenstein [1] on ninety-two premature infants, beginning with their blood findings at birth and continuing for considerable lengths of time. The premature infant at birth presents the high red blood cell count and the high hemoglobin usually found in full term [2] infants, while study of the blood smears shows more pronounced embryonic characters. His anemia appears first after the lapse of weeks or months, eventually becoming the marked and obstinate anemia so familiar in premature infants, which may be moderate or become very severe. In this connection it is of interest to note that of the ten cases of advanced and severe anemia studied by Evans and Happ,[3] six occurred in prematurely born infants, but the anemia described was in babies of several months or more of age. Finkelstein [4] observed that the number of anemic infants among premature babies was generally large from the fourth month on. Beside immaturity of the function of blood formation among these babies, iron has not been sufficiently stored in the liver, a function exercised in full term babies during the last three months of intrauterine life. Premature birth may explain the frequency of anemia in twins, while if they are full term and become anemic, it may be due to the fact that there was not iron [5] enough to go around.

To account for anemia in the early months of life, it is very natural to turn to the mothers of such infants. An explanation may be found in

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* Received for publication, Jan. 23, 1924.

1. Lichtenstein, A.: Hematological Studies Upon Premature Infants in Their First Year with Special Reference to Anemia, Svenska läk.-sällsk. handl. **43**:1533-1829 (Dec.) 1917. (Extensive Bibliography.)

2. Lucas, W. P., et al.: Blood Studies in the New-Born, Am. J. Dis. Child. **22**:525 (Dec.) 1921.

3. Evans, F. A., and Happ, W. M.: Secondary Anemia of Infants, Bull. Johns Hopkins Hosp. **33**:1-12 (Jan.) 1922.

4. Finkelstein, H.: Ueber die Anämien des frühesten Kindesalters, Berl. klin. Wchnschr. **48**:1829-1833, 1911.

5. Ashby, H. T.: The Relation of Iron to Anemia in Infancy and Childhood, Lancet **2**:150, 1912.

some mothers who have had acute illness while pregnant or who are suffering with tuberculosis or syphilis; in mothers of advanced age and weak constitutions; in neuropathic mothers, particularly with enteroptosis and anemia; and in mothers who have had repeated pregnancies at short intervals with abortions and hemorrhages.

Among other causes of anemia in the early months of life Finkelstein [4] gives the following: (1) a congenital form which is distinguished by absence of swelling of lymph nodes and spleen, with normal blood findings, except reduced hemoglobin and a moderate reduction in the number of red blood cells, and with good reaction to iron therapy; (2) an obstinate infantile anemia due to "plastic weakness in the function of blood formation, of which Virchow and Immerman speak," not readily influenced by iron administration, mixed diet, or other measures, while later the blood forming function gradually increases and the anemia disappears; (3) anemia of hereditary or family predisposition which hangs on in status quo in spite of therapy.

Holt and Howland [6] state that anemia "sometimes occurs in the first two or three months of life in a severe form without any discoverable cause."

Among discoverable causes may be mentioned infection of the young infant with pyogenic organisms, tuberculosis, syphilis, diphtheria, malaria, or other infections. Also traumatic and spontaneous hemorrhages including the hemorrhagic disease of the new-born. It is conceivable that the offspring of a mother addicted to the use during her pregnancy of a hemolytic drug such as acetanilid, might be anemic early in life, also a mother poisoned by mineral poison, benzol or other organic compounds.

Hemolytic jaundice may be manifest soon [7] after birth, and give rise to anemia. That rarer form of familial icterus,[8] sometimes spoken of as icterus gravis, is accompanied by severe, congenital anemia. In both of the latter, however, the icterus is a prominent symptom, while the anemia accompanies it.

The older the infant, the more numerous are the factors that operate to produce an impoverishment of the blood. The von Jaksch type of anemia is most common in the second half of the first year.

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6. Holt, L. Emmett, and Howland, John: Diseases of Infancy and Childhood, New York, D. Appleton & Company, 1922, p. 814.

7. McKelvey, J. P., and Rosenbloom, J.: Metabolism Study of a Case of Congenital Hemolytic Jaundice with Splenomegaly, Arch. Int. Med. **15**:227-238 (Feb.) 1915.

8. Buchran, and Comrie: J. Path. & Bacteriol. **13**:398-413, 1909. Rolleston, H.: Ten Postgraduate Lectures, Proc. Roy. Soc. Med., London 31-39, 1922; Practitioner **104**:1-7 (Jan.) 1920. Ylppö: Ztschr. f. Kinderh. **17**:334-362, 1918. Abt, I. A.: Familial Icterus of New-Born Infants, Am. J. Dis. Child. **13**: 231 (March) 1917.

Alimentary anemia[9] also occurs after the period which is being considered.

REPORT OF CASE

History.—F. O., a girl, white, born March 10, 1920, gave a negative family history. The mother, aged 27, had always been in excellent health. She had never used hemolytic drugs. A few weeks after the present baby was born the physical and laboratory examinations were normal (including Wassermann, blood, urine, and stool). The father, aged 33, an officer in the Regular Army, was in good health, and never had syphilis. Blood Wassermann was negative March 22, 1920. A sister of the patient, aged 3½ years, had always been in good health, was breast fed for four months, and was beyond the average child in development. There had been no other pregnancies. So far as known, there had been no contact with tuberculosis.

Labor began ten days prior to the estimated date of confinement, was eleven hours in duration, and without instrumental assistance. The baby weighed 7¾ pounds (3,516 gm.) and was described by the physician who delivered her as of normal, healthy appearance. When she was 11 days old, the nurse stated that she had been unusually pale from birth and that the pallor had been increasing steadily.

She cried well at birth and took the breast readily. March 11, twitchings of the right arm and forehead were noted. March 12, there were twitchings of the right side of the face, right arm and leg, lasting a couple of minutes, followed by the vomiting of "a large quantity of light fluid." Twitchings were observed repeatedly on the second and third days, lasting from one to four minutes. Temperature, the second morning was 101.6, evening, 98.6, and normal thereafter. Minimum weight 7 pounds (3,175 gm.) at 3 days of age. Cyanosis, skin eruptions, and snuffles were absent. Hemorrhages into the skin, from any of the mucous surfaces, and in urine and stools, were lacking.

The appetite was good, the infant having seven nursings in twenty-four hours.

The patient was first seen by me when 11 days old, the chief complaint being pallor of the skin and mucous membranes. The temperature was 97.8, the respirations and pulse being noted as rapid, the weight 7½ pounds (3,402 gm.) the length 20½ inches (51 cm.).

Physical Examination.—The general appearance was that of a strikingly pale baby with good nutrition and development, lying comfortably, breathing quietly but fast, expression calm.

The skin was fair, smooth, of normal turgor, moderately dry, with no signs of icterus, pigmentation, eruption or hemorrhage. The upper eyelids were somewhat puffy, the veins were not visible even on vigorous crying, which caused no reddening of the skin. No desquamation of palms, soles or elsewhere was noted.

The head was well formed and symmetrical. The eyes moved normally; the pupils were equal, medium in size, and contracted to light. The sclera was bluish white. The conjunctiva was very pale. The ears were strikingly pale and bloodless. The drum heads were pearly white, and presented normal land-

9. Hutchison, R.: Some Disorders of the Blood and Blood-Forming Organs in Early Life, Goulstonian Lectures, Lancet **1**:1253-1262, 1323-1333, 1402-1409, 1904. Kleinschmidt, H.: Ueber Alimentäre Anämie, Jahrb. f. Kinderh. **83**:221-258, 1916. Lehndorff, H.: Anemia in Children, Monatschr. f. Kinderh. **24**:1-44 (Oct.) 1922. Lucas, W. P., and Hoobler, H. R.: Study of Acute Secondary Anemias in Infancy, Am. J. Dis. Child. **26**:291-302 (Oct.) 1923. Morse, J. L.: Anemias of Infancy, J. A. M. A. **52**:455-463 (Feb. 6) 1909. Opitz, H.: Zur Pathogenese der Anämien im Kindesalter, Klin. Wchnschr. **1**:1769-1773 (Sept. 2) 1922. Poynton, F. J.; Thursfield, H., and Paterson, D.: The Severe Blood Diseases of Childhood, Brit. J. Dis. Child. **19**:57-80 (April-June) 128-143 (July-Sept.) 1922. Schwenke, J.: Ueber Schwere Anämien im frühen Kindesalter, Jahrb. f. Kinderh. **88**:181-203, 284-305, 356-385, 1918.

marks. The nose was well formed, unobstructed, with no excess of secretion. The septum and turbinates were very pale; no signs of hemorrhages. The lips were almost as pale as the white skin, moist, and free of ulcerations. The gums were pale, as were the buccal mucous membranes, tongue and pharynx; the tongue was moist, free of fissures and ulcerations.

There was no enlargment of the cervical, axillary, epithrochlear or inguinal lymph nodes, or of the thyroid gland. No cough was present or hoarseness of the cry. The chest was well formed and symmetrical. The respirations were rapid and of the combined abdominal and thoracic types. The lungs were well filled with air and otherwise normal. The heart apex was felt in the fourth space about the nipple line; no enlargement was made out, the sounds were of good quality; a soft, blowing, musical murmur was heard at the base, which was not transmitted. The pulse was very small, weak and rapid. The abdomen was at the same level as the thorax, rounded, soft and mobile.

The liver, which was not enlarged, was felt as a smooth mass below the costal margin. The spleen was barely palpable very slightly below the costal margin. The cord was off the navel, the base of which was very pale, not entirely healed and appeared healthy. The kidneys were not palpable. The joints were freely movable, and the muscles of the limbs and body were of good tone and strong. There were no swellings or tenderness along the bones or the joints. There was nothing abnormal to be seen in the genitalia.

Blood Examination.—March 22, the blood Wassermann was negative, the blood culture, of 1 c.c. of blood showed no growth, red corpuscles, 918,000, hemoglobin, 20 per cent., color index, 1+, white corpuscles, 29,200, stained smears of polymorphonuclear neutrophils 51.3 per cent., eosinophils 0.7 per cent., basophils 0.0, lymphocytes, 42.0 per cent., large mononuclears and transitionals 2.7 per cent., neutrophil myelocytes, 3.3 per cent.

Fragile white blood corpuscles ("smudges") were fairly numerous. Myelocytes and metamyelocytes, were both present but few in numbers. Several pathologic lymphoid forms were seen.

Nucleated red corpuscles, 10, apparently normoblasts, seen while counting 300 leukocytes; minimal degree of anisocytosis, a few macrocytes; an occasional poikilocyte was seen, extremely rare. The color was essentially normal except for an occasional pale macrocyte. Diffuse basophilia was fairly well marked more common in the cells, larger and paler than normal. Platelets were high normal or moderately increased. No parasites were seen. A probable diagnosis was of secondary anemia. The almost normal color of the red blood corpuscles associated with such a low red count was not to be expected.

March 23, the patient, at 12 days of age, had a transfusion of 100 c.c. of 0.25 per cent. citrated blood given by way of the longitudinal sinus. March 24, the color was greatly improved over that prior to transfusion. Blood examination showed the hemoglobin rose from 20 per cent. before to 45 per cent. after transfusion; the red blood cells rose from 918,000 before to 2,408,000 after transfusion; there were many nucleated red blood cells of both types; 1.5 per cent. of myelocytes; moderate changes in size, shape and staining of red blood cells were as before.

The urine which was of a pale, straw color, contained a trace of albumin, with negative sediment findings.

March 26, the spleen had become enlarged, and was now 1 to 1.5 cm. below the costal margin. The liver was of normal size.

March 27, the hemoglobin had fallen to 35 per cent. and the red blood count to 1,592,000 in four days. Fragmentation of red blood cells was observable (destruction of transfused corpuscles?).

March 28, Fowler's solution of arsenic, one-half drop, three times daily was started.

March 30, the weight was 7½ pounds (3,402 gm.). A second transfusion of 70 c.c. citrated blood was again given with a further notable improvement in color.

Comparison of Two Cases of Anemia in the New-Born

	Author's Case	*Ecklin's Case*
Family history	Healthy parents No deaths No miscarriages	Father had heart disease. Mother had grippe and bronchitis when six months pregnant; did not regain her strength. Several infantile deaths, one at 3 days, cause? one of convulsions at 6 months; one miscarriage; the infant born before the patient, died at 17 days of *icterus gravis familiare.*
Birth weight	7¾ lbs. (3,516 gm.)	2,870 gm. (6 lbs. 5 oz.)
Jaundice	Absent	Present from 1st to 16th days.
Spleen	Very slightly enlarged	Large soft mass 3 cm. below costal border.
Blood Examination at 12 Days of Age:		
Red blood cells	918,000	2,500,000
Hemoglobin	20 per cent.	32 per cent.
Color index	1.	0.64
White corpuscles	29,200	40,000
Red Blood Cells:		
Anisocytosis	slight	marked
Poikilocytosis	rare	frequency, moderate; irregularity, marked
Color	Normal: occasional pale macrocyte	many pale cells
Normoblasts	in moderate numbers	in large numbers
Megaloblasts	few	few
Basophilia:		
diffuse	marked	marked
punctate	slight	"not infrequent"
Reticulated red cells	4.6 per cent. [later]	not stated
White Blood Cells:		
Polymorphonuclears and myelocytes	55.3 per cent.	39.6 per cent.
Lymphocytes	42.0 per cent.	57.8 per cent.
Mononuclears	2.7 per cent.	2.6 per cent.
Total	100.0 per cent.	100.0 per cent.
Metamyelocytes	rare	4.0 per cent.
Myelocytes	3.3 per cent.	numerous
Lymphoid forms (pathologic)	a few	25.0 per cent.
Platelets	increased	not stated
Blood picture normal	within 6 months	within 7 months
Spleen, normal size	at 5 weeks	within 7 months

April 1, at 1 a. m., the temperature was 102.5, at 4 p. m. 101. The spleen was less than 1 cm. below the costal margin.

April 2, the mother and baby left the lying-in-hospital for home. The hemoglobin was 45 per cent.; red blood count, 2,000,000; white blood count, 10,000. Nucleated red cells were more numerous, also punctate and diffuse basophilia, slight poikilocytosis, and moderate anisocytosis. Myelocytes were 1.5 per cent.

From March 21 to April 2, all stools were inspected by me. None showed signs of hemorrhage. Generally they were dark green, with some mucus and a few, soft curds.

April 6, the urine was tested for pigments, with the following results: bile pigments (Huppert's test), negative; urobilin (Schlesinger's test), negative; carotin and lactochrome, negative; hemoglobin (1) guaiac, negative, (2) spectroscope, negative.

The stool test was: stercobilin (Schlesinger's test), positive. Blood test (1) guaiac test, negative; (2) spectroscope, negative.

April 7, freshly expressed beef juice made from rare steak, and expressed juice from cooked spinach, was given alternately to the baby during breast feedings. Fowler's solution was reduced to one-half minim twice daily. The hemoglobin was 50+ per cent.; red blood count, 2,248,000; white blood count, 13,650. The platelets were greatly increased. Myelocytes were 2.4 per cent. Changes in red blood count as last noted.

April 14, the weight was 8½ pounds (3,855 gm.), and the patient looked much better. The hemoglobin was 50 per cent., and the red cell count was slowly increasing. She acted in all respects like a normal baby but was still quite pale. The spleen was just palpable at the costal margin. The liver remained normal in size.

Blood examination for reticulated red corpuscles disclosed: fresh blood mixed with 0.4 per cent. salt solution (0.8 per cent. causing crenation) containing 1 part brilliant cresyl blue in 8,000 parts of salt solution, 92 reticulated red corpuscles seen in counting 2,000 red blood cells giving a count of 46 per thousand, or 4.6 per cent. (1 per cent. or less of reticulated corpuscles is normal).

From the age of 5 weeks on, the baby progressed in health, the spleen no longer being palpable, the hemoglobin and red cell count returning to normal inside of the next few months. She was breast fed until 10½ months of age, when she weighed 19 pounds 10 ounces (8,901 gm.), and was gradually transferred to a mixed diet. Her dentition was normal and her walking and talking little if at all delayed.

When she was 3 years, 8 months old, she was 38½ inches (96 cm.) tall, weighed 36 pounds (16.3 kg.), and was bright, active and healthy.

COMMENT

The case presented shows a severe anemia in an otherwise healthy new-born infant. The anemia was so severe at 12 days of age that the patient seemed to be in danger of death from it. Examinations of the blood showed various evidences of bone marrow activity and new blood formation, such as nucleated red blood cells of both types, poikilocytes, polychromasia, stippling, and macrocytes; an increased number of platelets; while on the part of the white blood cells, myelocytes, metamyelocytes and pathologic lymphoid forms, were present.

Evidences of blood destruction such as fragmentation of red cells, achromasia and shadow forms were unobservable. The absence of jaundice, including even slight yellowness of the sclerotics, and absence

of urobilin and hemoglobin from the urine, were confirmatory of lack of excessive blood destruction, so far as these signs are valid evidence. The spleen enlarged noticeably during the days when the red blood count and hemoglobin were falling, after the first transfusion.

Likewise, the spleen remained temporarily slightly enlarged following the second transfusion, but by the age of 5 weeks the spleen was no longer palpable. Blood formation was so well under way from this time on as to show steadily increasing hemoglobin and red cells and diminishing white cells. A striking and unexpected factor in this case was a normal color index. The red cells appeared to have their full quota of hemoglobin. Increase in hemoglobin continued quite as rapidly as increase in red cells, an occurrence different from what usually happens, namely, an increase in the number of red cells at a more rapid rate than increase of hemoglobin, giving a color index of less than 1.

A color index of 1 was present in this patient when the anemia was most marked at 12 days of age, and persisted while the anemia was disappearing.

The muscular twitchings of the right side present during the first three days of life, with vomiting and fever once, may have been due to intracranial hemorrhage, but there was no cyanosis or rigidity noted and the baby breathed normally and nursed well. Subsequently, no signs of cerebral damage made their appearance. If intracranial hemorrhage caused these symptoms, the amount of blood extravasated must have been small.

Ecklin [10] reported a marked but less severe anemia in a new-born infant, a comparison of which, with the case here presented, discloses many points of similarity. This case of Ecklin's is the only one which has been found, although prolonged search has been made at the Surgeon-General's Library.

Doubtless other similar cases of anemia in the new-born have occurred without finding their way into medical literature, but they can hardly be common. All of the discoverable causes of such an anemia seem to have been excluded: on the part of the mother, acute illness during pregnancy, debility, hemolytic drugs and transmissible disease; on the part of the infant, prematurity and debility, infectious diseases, hemorrhages, and jaundice both hemolytic and icterus gravis.

No explanation of the cause of it can be offered. The patient's recovery was complete, and the subsequent development during three and a half years has been normal.

1612 I Street, N. W.

10. Ecklin, T.: Ein Fall von Anämie bei einem Neugeborenen, Monatschr. f. Kinderh. **15**:425, 1919.

ACUTE FATTY ENLARGEMENT OF THE LIVER IN INFANTS

REPORT OF FOUR CASES WITH NECROPSY EXAMINATION *

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Acute fatty enlargement of the liver after the new-born period is comparatively infrequent. During the last year we have had the opportunity of seeing four cases, the infants all being under 1 year of age. In two of these cases the etiology for the liver condition was evident; one infant had ingested some insecticide paste which contained phosphorus; in the other arsenic was the toxic agent, demonstrated after a chemical examination of the organs. In the two remaining cases the etiology was unknown; their ages were 4½ months and 11½ months, respectively. Both children were almost entirely breast fed at the time of admission to the hospital. There was nothing characteristic in the clinical history. One child had had a convulsion five weeks previously; the other had had intermittent vomiting for the last two months. On physical examination these fairly well developed children were acutely ill with a moderate rise in temperature, a mild degree of generalized icterus and a tremendous enlargement of the liver, the right lobe extending below the crest of the ilium, the lower edge of which could easily be felt on rectal examination.

Phosphorus, arsenic and chloroform are the most frequent causes of rapid fatty enlargement of the liver. The other conditions which may cause acute liver enlargement, but in which the liver rarely, if ever, reaches these tremendous proportions are (1) acute intestinal intoxication, (2) acute infection, such as pneumonia, (3) erythema desquamativum (Leiner) and pemphigus; (4) miscellaneous conditions, such as tuberculosis, syphilis and leukemia. Very obese normal infants often have a fairly large liver.

MacCallum [1] believes that the deposit of fat in the liver is one of infiltration rather than one of degeneration. Unless there is a true necrosis of liver tissue such as is found in acute yellow atrophy, fat infiltration is the better term. McNee,[2] using the old terminology,

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* Received for publication, Jan. 23, 1924.

* From the pediatric service, Mount Sinai Hospital.

1. MacCallum, W. G.: Text Book of Pathology, Philadelphia, W. B. Saunders Company, 1916.

2. McNee, J. W.: Brit. M. J. **2**:1055, 1922.

believes fatty degeneration to be a reaction of the cells to an injury which is greater in severity than that producing cloudy swelling but less severe and slower in action than that causing actual cellular necrosis.

A marked lipemia is one of the findings which should be emphasized. In one of the cases (Case 1) the blood serum fat was over 4 per cent. This excessive fat undoubtedly has its origin in the fat depots in the body, i. e., the subcutaneous tissues. There must have been some disturbance in the fat transport. Leathes [3] has shown that this lipemia occurs only when the glycogen content of the liver is very low. Bloor [4] believes "that the cause of the lipemia is a flooding of the blood with amounts of fat greater than the normal mechanism can take care of at once." In some cases, such as acute nutritional disturbances, the liver cells receive an inadequate amount of carbohydrate and therefore must obtain and burn a much larger amount of fat to supply their energy needs; in fact, all the tissues under these circumstances must supply their energy requirements by an inordinate consumption of fat. For this purpose the subcutaneous and other fat depots are mobilized, and there is excessive fat transport as evidenced by lipemia. The liver cells and often Kupffer's cells become filled with fat. This is one method by means of which fat accumulates in the liver cells. The second method may be a diminished oxidation within the liver cell and the intracellular accumulation of fat because its rate of utilization is lower than the rate at which it is supplied. The fatty accumulation in the liver in passive congestion is another example of the latter method.

The urine in Case 1 contained glucose, the blood sugar being normal. We are unable to state the significance of this finding in relation to the fatty liver. There was no leucin or tyrosin in the urine.

In Cases 1 and 2, chemical examination of the organs failed to reveal any traces of arsenic or phosphorus; yet it is well known that even in experimental phosphorus poisoning, phosphorus cannot be found in the organs after forty-eight hours. On the other hand, phosphorus may act for a long time after the initial ingestion. Remembering that both of these children were being breast fed, it is important to know that neither one of the mothers had been taking any drugs. The other common condition of fatty enlargement of the liver such as acute intestinal intoxication, syphilis or tuberculosis can be excluded in our cases from the chemical, serologic and necropsy findings.

It has been shown experimentally [5] that the use of glucose intravenously and by mouth has prolonged the life of animals poisoned with

3. Leathes, J. B.: Harvey Lectures, 1908-1909.

4. Bloor, W. R.: J. Biol. Chem. **49**:201 (Nov.) 1921.

5. Davis, N. C., and Whipple, G. H.: Liver Regeneration Following Chloroform Injury as Influenced by Various Diets, Arch. Int. Med. **23**:711 (June) 1919. Simonds, J. P.: The Mechanism of the Protective Action of Carbohydrate Diet in Phosphorus and Chloroform Poisoning, Arch. Int. Med. **23**:362 (March) 1919.

phosphorus. This indicates that an inadequate supply of glucose in the liver cells is responsible for the presence of increased amounts of fat as previously explained. It would therefore seem reasonable to try glucose in these cases with the possible chance of keeping the infant alive.

REPORT OF CASES

CASE 1.—*History.*—A boy, aged 4 months, was admitted to the hospital with a history of having had convulsions five weeks ago and again ten days ago. The patient was the first child and the first pregnancy, and weighed at birth 8½ pounds (3,955 gm.), at 14 weeks he weighed 12 pounds (5,443 gm.). He was breast fed entirely for six weeks and thereafter was given an occasional supplementary milk feeding. The child was perfectly well up to five weeks before admission when he had had a general convulsion lasting a few minutes. The mother attributed this to having given him a little albumen a few hours before. The child was well, gaining normally up to ten days before admission when he again had a convulsion lasting a few minutes. A lumbar puncture was made at that time which was said to have contained no cells. Since the puncture the patient had a low grade temperature, up to 102. At time of admission he was having six to seven loose bowel movements a day, and had vomited once.

Physical Examination.—The infant was fairly well developed, weighed 10 pounds (4,535 gm.) and appeared acutely ill. The skin and sclera were faintly icteric; the fontanel was not bulging. The throat, lungs and heart were normal. The abdominal examination disclosed a large smooth mass which extended below the crest of the ilium in the right axillary line and almost below to the level of the umbilicus in the left axillary line. A notch could be felt in the midline. This mass was undoubtedly the liver. Extending from under the free border of the liver in the left axillary line another mass could be felt which was probably the spleen. The lower portion of the right lobe of the liver could easily be felt on rectal examination. The temperature on admission was 106.

Laboratory Examination.—The Pirquet and Wassermann tests were negative. The urine contained a trace of albumin, a marked reaction for sugar and, miscroscopically, contained a few hyaline casts. The blood chemical examination showed a milky serum. Urea nitrogen, 11.2 mg. per hundred cubic centimeters; cholesterol, 0.436 per cent.; sugar, 0.085 per cent.; serum fat, 4.06 per cent. The Van den Bergh test for bilirubin was positive by the direct and indirect test. The blood count was, white blood cells 11,600; polymorphonuclears, 18 per cent.; eosinophils, 3 per cent.; lymphocytes, 75 per cent.; myelocytes, 2 per cent.; myeloblasts, 2 per cent. The red cells showed a mild degree of anisocytosis.

Course.—The patient's condition gradually grew worse, the temperature ranging from 102 to 105, and he died five days after admission.

Necropsy.—The infant was 23 inches (58 cm.) long with an icteric tint to the skin. The lungs were well aerated with a few small petechiae under the pleura. The heart showed no valvular defects, the muscle was pale on section. There were a few small petechiae under the pericardium. The spleen was large, weighing 19.5 gm., and was deep red on section and sprinkled with lighter spots. The liver weighed 740 gm., was mottled, pale yellow and pink. The cut surface showed pale yellowish spots, surrounded by pink areas; the section was distinctly greasy. The gallbladder was normal. The adrenals were small. The kidney cortex was pale and swollen. The Peyer's patches of the intestine were hypertrophied. The brain was wet, the vessels injected.

Microscopic Examination.—The lungs showed edema and congestion. The liver showed an intense parenchymatous degeneration and an enormous fatty infiltration of the liver cells. There were no areas of necrosis or cellular infiltration. In a frozen section stained for fat, liver cells of the inner two-thirds of the lobule were filled with fat globules; the cells of the inner one-third had less fat. Spleen: the malpighian bodies were hypoplastic. The pulp showed only moderate cellular increase and extrasinusoid congestion. The kidney showed tubular degeneration involving chiefly the convoluted tubules. Epithelial cells of the latter were swollen and the cytoplasm was transparent and hydropic in appearance. The tubules of the medulla showed slightly parenchymatous degeneration. A frozen section stained for fat showed degenerative changes in the convoluted tubules of the cortex, but no fat. Brain cells were edematous. Chemical examination of the liver showed no traces of arsenic or phosphorus.

CASE 2.—*History.*—A girl, aged 11 months, had fever for nine days. She was the first child and the first pregnancy, born at full term and breast fed up to the time of admission to hospital. For two months before admission the patient would vomit occasionally for a few days. Nine days before, she had a period of vomiting, at which time the temperature was 102. The mother was told by her physician that the baby's urine contained pus cells.

Physical Examination.—The infant was well developed, and acutely ill, with an icteric tint to the sclerae. The fontanel admitted one finger. The lips were dry, and covering the tongue, buccal mucous membrane and palate were small whitish follicles (thrush?). The lungs revealed a few coarse râles but no bronchial breathing. The abdomen revealed a large mass, probably the liver, reaching below the pelvic brim on the right side; the spleen was not palpable. There was edema of both legs. Small petechiae could be seen over the legs, left elbow and right forearm. The temperature was 103 on admission.

Laboratory Examination.—The Pirquet and Wassermann tests were negative. The urine contained no albumin, sugar or pus. It was negative for bile, leucine and tyrosin. The blood examination was, hemoglobin (Kuttner's) 75 per cent.; red blood cells, 4,400,000; white blood cells, 37,000; polymorphonuclears, 37 per cent.; lymphocytes, 60 per cent.; mononuclears, 3 per cent. There were no abnormal cells; the bleeding time was four minutes. Blood culture was negative; throat culture was negative for diphtheria. The roentgenogram of the lungs was normal. A chemical examination of medicine the child had been taking before admission was negative for phosphorus and arsenic.

Course.—The condition of the child became rapidly worse, and she died thirty-six hours after admission.

Necropsy.—Examination showed a well developed infant. The dorsum of both feet and forearm showed a few petechial spots (from 1 to 2 mm. in diameter). The thymus was not enlarged. The lungs showed a few subpleural hemorrhages and on cut section a moderate congestion. Heart showed a few precordial petechiae. The heart muscle was brown and pale. The peritoneal cavity contained 30 c.c. of clear yellow fluid. The liver was enlarged, the right lobe reached beyond the crest of the ilium. It was soft, friable and grayish-yellow, and extremely fatty. The spleen was somewhat enlarged, firm and dark red. The gastro-intestinal tract was normal; no lymphoid hyperplasia. The cortex of the kidney was of normal thickness and had a pale grayish-yellow appearance. The glomeruli did not stand out. The medulla, by contrast, had a dark red color. There was no change in the adrenals. The brain was normal.

Microscopic Examination.—The heart muscle striations were indistinct. The lungs had peribronchial round cell infiltration in places. The liver had tremendous fat infiltration through all portions of the lobules, with no area of necrosis. The spleen pulp showed congestion and cellular increase. Venous

sinuses were widely dilated. The kidney showed parenchymatous degeneration of tubules with a great deal of fat deposit in the latter. The pancreas was normal, and the brain normal.

CASE 3.—*History.*—A boy, aged 5 months, had a history of cough for four days and loss of consciousness for one day. The patient was born at full term, of normal delivery. He was breast fed for one month; then on a milk mixture, and was gaining normally. Five days before admission, cough and drowsiness were noted. There was no rise in temperature. One day before admission respiration had been "grunting," and for six hours the patient had been comatose.

Physical Examination.—The patient, a well developed infant, was cyanotic and acutely ill. The fontanel was not bulging. The pharynx, heart and lungs were normal. The abdomen was lax. The right lobe of the liver reached to the brim of the pelvis. The spleen was not felt. The child died soon after admission.

Necropsy.—The heart and lungs showed no gross changes. The liver was large, extremely pale, fatty and firm; the spleen was small and soft. The stomach and intestines were normal. The kidney was small and lobulated, the capsule stripped easily; on section, it was congested with cloudy swelling. The pancreas and adrenals were normal. The brain was congested; with edema of the meninges.

Microscopic Examination.—The liver change was similar to Cases 1 and 2. A chemical examination of it revealed traces of arsenic.

CASE 4.—*History.*—A girl, aged 1 year, was admitted to hospital with a history of vomiting for three days and convulsions for one day. The family and developmental history was negative. Three days before admission the patient ingested a potato on which roach paste had been spread. The following morning (twelve hours later) the child vomited whenever fed and was drowsy. There was no diarrhea or bloody stools. The stupor increased and during the previous day she had had frequent convulsions.

Physical Examination.—A well developed child was noted, with frequent tonic spasms of the body; the pupils reacted sluggishly to light; the fundi were normal. The pharynx, heart and lungs were negative. The liver reached 6 cm. below the costal margin on the right side; the spleen was not felt.

Laboratory Examination.—White blood cells, 20,000; polymorphonuclear, 62 per cent.; lymphocytes, 29 per cent.; mononuclear, 9 per cent. The urine contained a trace of albumin, no sugar and a few hyaline and granular casts. No bile was present.

Course.—The child died a few hours after admission, with a temperature of 103.

Necropsy.—There were no petechiae, jaundice or icterus. Lungs, heart and spleen were normal. The liver was large and yellow; of normal consistency. The intestines showed small scattered areas of slight congestion of the mucosa. There were no ulcerations anywhere. Both kidneys had increased in size. On section, the cortex was normal in size, yellow in color and streaked with longitudinal red lines. The meningeal vessels of the brain were congested and the surface of the brain slightly edematous.

The heart muscle fibers were atrophic with a great deal of round cell infiltration between the fibers. The lungs showed evidences of bronchopneumonia.

The entire liver parenchyma was replaced by small and large fat droplets and some cells showed an early necrosis. This was an acute process. A fat stain showed fatty infiltration with some round cell infiltration.

The spleen showed degenerative changes of malpighian corpuscles with fatty infiltration into the centers. The stomach showed a necrosis of the mucosa.

SUMMARY

1. Four cases are presented of acute fatty enlargement of the liver in infants, with a clinical picture of severe toxemia.

2. Metallic poison should always be borne in mind as an etiologic factor in patients acutely ill that show very large livers.

3. Examination of the blood for fat may often reveal lipemia as an aid in diagnosis of fatty infiltration of the liver.

4. The administration of glucose may be of some help in treatment.

RÉSUMÉ OF THE LITERATURE FOR 1921 ON TUBERCULOSIS IN CHILDHOOD*

DIAGNOSTIC TESTS AND SEROLOGY

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Levinson [1] studied 300 children, most of whom had come in contact with tuberculosis. One hundred and forty-one reacted positively and eighty-three reacted negatively to the tuberculin test; the diagnosis of the condition of the remaining seventy-six was doubtful. Most of the children with positive reactions had become infected from the fathers. Of the group of 141 children, thirteen presented symptoms of active tuberculosis, and 128 of latent tuberculosis. Only three of those with active symptoms had active pulmonary lesions. Ninety-eight per cent. of those with latent tuberculosis had no subjective symptoms, but 90 per cent. were under weight. In 75 per cent. hilum dulness and whispered bronchophony to the seventh dorsal vertebra were present. There was a shadow in the roentgen-ray plates in the region of the hilum, and one or more calcified areas in the substance of the lung. The Eustace Smith's sign was very infrequent. Levinson believes that a positive tuberculin reaction in children should establish a diagnosis of tuberculous infection, and that the classification of this type of infection depends on the subjective and objective symptoms, and on the roentgen-ray findings.

Dietl [2] performed the Pirquet test on a number of children having symptoms suspicious of tuberculosis, and found a surprisingly small number of positive reactions. He thinks this is due to a lowered, general or cutaneous, sensitiveness to tuberculin. A positive intracutaneous test means an active tuberculosis only when small doses of tuberculin are used, and in the presence of definite lung findings. A negative reaction, however, when larger doses of tuberculin are used excludes tuberculosis.

Debré, Paraf and Dautrebande [3] have shown that a negative tuberculin test in an infant suffering from tuberculosis is owing to the fact that the test was being performed during the antiallergic period, and a diagnosis cannot be determined until a series of tests are made over a sufficiently long period of time (four months). These authors have

* Received for publication, Feb. 26, 1924.

* Part of this material was collected by the late Dr. May Michael.

1. Levinson, A.: Med. Rec. **99**:773 (May 7) 1921.
2. Dietl, K.: Monatschr. f. Kinderh. **19**:422 (Feb.) 1921.
3. Debré, R.; Paraf, J., and Dautrebande, L.: Ann. de méd. **9**:443 (June) 1921.

proved conclusively that tests made in this way cannot provoke a reaction in a healthy infant or modify the antiallergic period in a tuberculous one.

Kretschmer [4] studied the Pirquet test in 180 children under 14 years of age, with a history or clinical findings of tuberculosis. He compares his results with those of Klose and Synwoldt in the following table:

Cases	Klose 120	Synwoldt 80	Kretschmer 180
Positive reactions (per cent.)	62.5	49	42.2
Old tuberculin reactions	9.33	1.25	28.9
Bovine tuberculin reactions	5.34	35.00	7.8
Old tuberculin greater than bovine	29.33	—	18.4
Bovine greater than old tuberculin	13.33	5.00	7.9
Bovine and old tuberculin equal	42.67	58.75	36.8

Kretschmer states that the percentage of positive Pirquet reactions among the children of Berlin is very low because of the extant malnutrition which confers immunity.

Gittings and Donnelly [5] published statistics on the Pirquet reaction, obtained from the records of the last ten years in the Children's Hospital of Philadelphia. Their results demonstrate the high percentage of tuberculous infection and the comparatively low incidence of recognizable clinical tuberculosis in childhood. The authors emphasize the importance of at least one repetition of the tuberculin test, if the first proves negative.

Furstner-Risselada [6] reports the results of the Pirquet test on 1,504 schoolchildren in Haag, a city in Holland with 360,000 inhabitants. Positive reactions were obtained in 399 children as follows: In the group of 591 children, aged 6 years, 119 positive reactions were obtained; of 278 children, aged 7 years, sixty-seven reacted positively; of 139, aged 8 years, thirty-nine gave positive reactions; of 142, aged 9 years, there were forty-five with positive reactions; of 123, aged 10 years, there were fifty-three with positive reactions; of 115, aged 11 years, there were thirty-five with positive reactions; of eighty-five, aged 12 years, there were thirty-five with positive reactions, and of thirty-one children, aged 13 years, there were six with positive reactions. These figures are much lower than those of Hamburger and Monti, probably because their patients were children in the polyclinic, whereas those observed in this study were schoolchildren chosen at random.

Salmony [7] attempted to ascertain whether localization, anemia, hyperemia, or water content of the skin had any influence on the Pirquet reaction. The tests were made on children from 6 months to 14 years

4. Kretschmer, M.: Deutsch. med. Wchnschr. **47**:465 (April 28) 1921.
5. Gittings, J. C., and Donnelly, J. D.: Arch. Pediat. **38**:78 (Feb.) 1921.
6. Furstner-Risselada, A. M.: Monatschr. f. Kinderh. **21**:271 (June) 1921.
7. Salmony, L.: Arch. f. Kinderh. **69**:454 (June) 1921.

of age. To determine the effect of localization, tests were made above and below the elbow joints, above the wrist, on the extensor and flexor surfaces of the forearm, and on the chest. The reaction above the wrist was least marked and the reaction of the test 5 cm. below the elbow most intensive. The Pirquet reaction was less marked when the hyperemia was produced with mustard plasters, vacuum cups or sand-bags, but was increased when produced with Bier's pump. The reaction was increased in the anemic areas. Increased moisture content of the skin was effected by the Priessnitz compress and by means of cod liver oil. Lessened water content was produced by the use of alcohol. No rule could be formulated with regard to the effect of this condition on the reaction. The author draws the following conclusions: Local factors have a decided influence on the intensity of the Pirquet reaction, but they never change the reaction from positive to negative or the reverse. Increasing the rapidity of the blood stream causes a less marked reaction, slowing the blood stream intensifies the reaction. Complete stasis of the blood stream intensifies the reaction to the greatest degree.

Kretschmer [8] reports his experience with the new diagnostic tuberculin, or Moro's test. This consists of old tuberculin to which is added a concentrated extract of the original culture and also bovine tuberculin. Three hundred tuberculous children, and also children in whom tuberculosis was suspected, were vaccinated by Kretschmer with this preparation. The following results were obtained: Reactions positive and similar to old, diagnostic tuberculin, 103 cases; reactions negative to both tuberculins, 131 cases, reactions more positive to old tuberculin, eighteen cases; reactions more positive to diagnostic tuberculin, twenty-four cases; reactions positive only to old tuberculin, fifteen cases; to diagnostic tuberculin only, nine cases. Kretschmer, therefore, could not see any advantage in diagnostic tuberculin over the old tuberculin.

Meyer [9] made comparative tests with old tuberculin and Moro's diagnostic tuberculin on 245 children from 2 to 14 years of age. One hundred and twenty-six children gave positive reactions. Moro's old tuberculin gave 30 per cent. positive reactions; Höchst's old tuberculin 75 per cent., and Moro's diagnostic tuberculin 98 per cent. Not only were there more positive reactions with Moro's preparation, but the reactions were more definite and the area of the erythema and induration more intense.

Brüning [10] has collected statistics in regard to the frequency of a positive Pirquet reaction on children of the well-to-do. He examined 350 children of all ages who came to him for treatment of conditions other than tuberculosis. In ninety-one, there were positive reactions.

8. Kretschmer, M.: München. med. Wchnschr. **68**:852 (July 8) 1921.
9. Meyer, L.: München. med. Wchnschr. **68**:1286 (Oct. 7) 1921.
10. Brüning, H.: Jahrb. f. Kinderh. **96**:286 (Nov.) 1921.

Von Hayek,[11] basing his opinion on two years' experience in treating 400 tuberculous children, believes that the percutaneous injection of tuberculin, according to the method of Petruschky, gives the best results and is the easiest way of administering the tuberculin.

Korbsch [12] obtained positive cutaneous reactions with freshly drawn undiluted cerebrospinal fluid in two cases of tuberculous meningitis. Numerous controls with fluid from patients with pulmonary tuberculosis gave negative results. It is true, however, that tests with cerebrospinal fluid from patients with cerebral affections other than tuberculosis also gave positive reactions. The test could not, therefore, be regarded as specific for tuberculous meningitis.

Fischer [13] applied the intradermal tuberculin test at monthly intervals to 200 tuberculous subjects of different ages. The test was more sensitive when the diluted tuberculin was mixed with the patient's own blood serum. This test, applied to forty patients who were injected by the Mantoux technic, produced no lung, focal, or general response, but the skin reaction was a papule from 1 to 20 mm. in diameter. The skin reaction corresponded more closely to the course of the case, and seemed less dependent on the condition of the skin and location of the injection.

Dietrich [14] prepared a special tuberculin, and produced essentially different reactions with intracutaneous tests than with subcutaneous tests. He concluded that the reaction mechanism of intracutaneous tests and subcutaneous tests are essentially different.

Feer [15] describes a simple cutaneous tuberculin test in which he prepares the sterilized skin by rubbing and then applies the tuberculin.

Vitón [16] argues that occult, dormant, and masked infection with the tubercle bacillus is extremely frequent, and that most of the infections in adults are merely the transient flaring up anew of this infection acquired in early childhood. Treating the manifestations with extremely minute doses of tuberculin benefits the primary infection. As this factor disappears the other symptoms become attenuated or vanish.

Hamburger and Peyrer [17] describe the negative and positive phases of susceptibility according to Wright's opsonins. In another article [18] they discuss the negative phase of sensitiveness to tuberculin.

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11. Von Hayek, H.: Wien. klin. Wchnschr. **33**:768 (Aug. 26) 1920; ibid, **33**:798 (Sept. 2) 1920.
12. Korbsch, R.: Med. Klin. **17**:816 (July 3) 1921.
13. Fischer, C.: Schweiz. med. Wchnschr. **51**:592 (Oct. 27) 1921.
14. Dietrich, W.: Deutsch. med. Wchnschr. **47**:406 (April 14) 1921.
15. Feer, E.: München. med. Wchnschr. **68**:1050 (Aug. 19) 1921.
16. Vitón, J. J.: Semana méd. **28**:473 (April 21) 1921.
17. Hamburger, F., and Peyrer, K.: Wien. klin. Wchnschr. **34**:157 (April 7) 1921.
18. Hamburger, F., and Peyrer, K.: Wien. klin. Wchnschr. **34**:280 (June 9) 1921.

Zinsser [19] reports experimental investigation and a study of the principles of intradermal tuberculin reactions.

Kharina-Marinucci [20] performed the complement fixation test on 227 tuberculous infants. Three antigens were used, a watery emulsion, an hydro-ether-alcohol extract of the emulsion, and Koch's old tuberculin. The author examined 400 serums and concluded that the test had practically no value in the diagnosis of infantile tuberculosis.

In a later work, Kharina-Marinucci [21] reports the results of sero-agglutination tests in children. Ninety-five per cent. of 235 tuberculous children gave a positive response when the test was applied to the avian variety of tubercle bacillus. Agglutination occurred at from 1:25 to 1:100 in the majority, but in five cases at from 1:200. The negative responses were in the most incipient or in the most advanced cases. The titer sometimes grew higher as the child improved and lower as the disease progressed. The findings confirm those of Di Cristina, who first suggested the use of the avian variety for the purpose. The special localization of the tuberculous process did not seem to affect the response.

Ribadeau-Dumas, Cuel and Prieur [22] found, by means of the complement fixation test performed on tuberculous mothers and their infants, that women with open tuberculosis can transmit antibodies to the infant but that the antibodies disappear from the infant's blood shortly after birth.

Epstein [23] performed intracutaneous tests with the milk of tuberculous cows, and apparently confirmed the presence of a tuberculous antigen in the milk. He injected 0.1 c.c. of milk into the skin on the inner side of the forearm of children affected with tuberculosis, who had given a positive reaction to tuberculin. As a control, certified milk, milk from nontuberculous cows, and dry milk were injected into the other arm. A positive result was always obtained in tuberculous children with milk of tuberculous cows (thirty-five injections) whereas a negative result was obtained with the other milks (twenty-six injections). Epstein, moreover, showed that milk of tuberculous cows gave negative reactions when injected into children who had a negative Pirquet test. The injection of the milk of tuberculous cows frequently caused also a torpid Pirquet test to flare up and become markedly positive. From the results of these experiments the author concludes that the milk of tuberculous cows contains antigens not present in the

19. Zinsser, H.: J. Exper. Med. **34**:495 (Nov.) 1921.
20. Kharina-Marinucci, R.: Pediatria **29**:500 (June 1) 1921.
21. Kharina-Marinucci, R.: Pediatria **29**:529 (June 15) 1921.
22. Ribadeau-Dumas, M. M.; Cuel, and Prieur.: Rev. internat. de la tuberc. **2**:378, 1921.
23. Epstein, B.: Jahrb. f. Kinderh. **95**:64, 1921.

milk of nontuberculous cows, although these antigens are not in the milk of every tuberculous cow, and the severity of the disease does not determine their presence because they occur in animals with only a positive tuberculin test as the evidence of tuberculosis.

Epstein [24] also made 1,800 parenteral injections of normal horse or sheep serum in forty-six tuberculous children, varying in age from 3 months to 14 years. He wished to study the influence of parenteral administration of foreign protein on the tuberculous organism, and the syndrome known as serum disease. He found that, contrary to the general opinion, the parenteral administration of foreign serum did not cause fever in tuberculous children, as did the injection of old tuberculin or milk. Serum reactions, however, did occur. With the administration of 10 c.c. of serum biweekly, 65 per cent. of the children had serum reactions. Severe reactions resembling shock occurred four times directly after the injection. Repeated injections caused increased sensitiveness, and the patients did not become accustomed to the injections as they did to the injections of milk and tuberculin.

In order to judge the value of the complement fixation reaction in tuberculosis, Sévi [25] tested fifty-four institutional children from 7 to 14 years of age, none of whom showed evidence of any illness. In fifty children the test was negative, in four positive. Further examination of the four who gave positive reactions revealed tuberculous lesions, and the finding was confirmed by roentgen ray.

Cook [26] has made a study of the complement fixation test for tuberculosis in children. A total of 1,855 fixation tests were performed on 1,556 children. By a careful clinical study of each case these children were separated into four groups, namely: manifest, masked, suspected and healed tuberculosis. In the first group there was no doubt concerning the diagnosis of an active tuberculosis. The results of the complement fixation test in this group show a very definite relation to the age of the child. During the first year no positive fixation reactions occurred; from 2 to 4 years about 40 per cent. of the children reacted positively to the test; from 4 to 6 years this percentage increased to 56, and above 6 years over 80 per cent. showed positive reactions. The children of the masked tuberculosis group gave positive complement fixation reactions in the same proportion as those with manifest tuberculosis. The test is consequently of great aid in calling attention to this common and frequently overlooked type of tuberculosis in children. About half of the group classified as "suspected tuberculosis" showed

24. Epstein, B.: Jahrb. f. Kinderh. **95**:52, 1921.
25. Sévi, J.: Presse méd. **29**:484 (June 18) 1921.
26. Cooke, J.: Complement Fixation for Tuberculosis in Children, Am. J. Dis. Child. **21**:78 (Jan.) 1921.

positive fixation reactions. Twenty patients with healed tuberculous lesions were examined. Only two of this group gave positive reactions.

Since these children were all over 4 years of age, the results give additional evidence of the association of active tuberculosis with a positive fixation reaction. In concluding his study, Cooke points out that a positive fixation reaction is associated in a large majority of cases with a tuberculous lesion that is pathologically, if not clinically, active, and consequently, any patient giving a positive reaction should not be considered free from active tuberculosis without a thorough study.

Gibson and Carroll [27] studied the auto-urine test in forty cases of tuberculosis among children and adults. All patients with bone lesions were allergic and all reacted distinctly to the auto-urine test. No conflicting results were obtained. Every patient who was sensitive to tuberculin and had signs of active tuberculosis gave a positive auto-urine reaction. The urine of patients with active lesions, who were not sensitive to tuberculin, gave positive reactions when injected into allergic persons. Negative reactions in allergic patients bore out the opinion that they had no active lesions.

Kotzulla [28] tested fifty children to ascertain whether a positive auto-urine reaction speaks for an active tuberculosis and a negative reaction for nonactivity. He divided his material into three groups. Group 1 consisted of children free from tuberculosis or with nonactive lesions. All these gave negative reactions. Group 2 consisted of children with active lesions and these all gave a positive reaction, strong, or weak, according to the degree of activity. Group 3 consisted of children with bronchial gland tuberculosis, with positive but weak reactions. Group 4 contained children suspected of active tuberculosis, and in all of these a positive auto-urine test corresponded with the clinical evidences of activity. Kotzulla believes the auto-urine test is specific for active tuberculosis, except in cases associated with insufficiency of both kidneys, and with its aid the diagnosis of the onset of an active lesion can be made earlier than by physical or clinical methods.

Nasso [29] concludes from the results in ten nontuberculous and in fifty-three tuberculous children that the auto-urine test is specific for tuberculosis. He has simplified Wildbolz' technic in that he merely evaporates 100 gm. of urine in a broad basin at a temperature of 60 or 63 C. (140 to 145.4 F.) for three or four hours to reduce it to one-tenth of its original volume. The salts adhere to the bottom of the basin and two or three drops of the concentrated urine are injected as for the intradermal tuberculin test. Nasso also injected twenty-six

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27. Gibson, C. B., and Carroll, W. E.: The Auto-Urine Test for Active Tuberculosis, J. A. M. A. **76**:1381 (May 21) 1921.

28. Kotzulla, O. H.: Ztschr. f. Kinderh. **29**:93 (April) 1921.

29. Nasso, I.: Pediatria **29**:690 (Aug. 1) 1921.

children with their own serum, evaporated to one-tenth its original volume in a watch glass. He prefers this serum to the urine, as the injections are never painful and never induce necrosis, although the reaction is not quite so pronounced as with the urine.

Alexander [30] tested ninety-one patients, mostly children, for the Wildbolz auto-urine reaction. Among them were seventy-six cases of pulmonary tuberculosis, one case of cervical gland tuberculosis, one of tuberculous spondylitis, and thirteen cases in which no tuberculosis could be found. Fifteen of the patients with active pulmonary tuberculosis gave a negative auto-urine reaction; two gave, at first, a positive and later a negative reaction; and three gave first a negative and then a positive reaction. In these an improvement had occurred in the interval. In eleven patients with active pulmonary tuberculosis the test was markedly positive, in two weakly positive, and in two undetermined. In ten patients on whom the test was repeated it became more markedly positive and always so in children who were improving. The author concludes that a negative auto-urine reaction does not exclude an active tuberculosis. There is no parallelism between the intracutaneous and the auto-urine tests. The tests must be made with concentrated urine, and the best results are obtained by evaporation to one-tenth its volume in a vacuum.

Widmaier [31] calls attention to the value of the Pandy reaction in tuberculous meningitis. The test consists of adding 1 c.c. of phenol (1 part phenol crystals to 15 parts water) to 1 drop of cerebrospinal fluid. A cloudy, bluish white precipitate forms when the globulin is present in abnormal amounts. Widmaier found that the Pandy reaction was more reliable than the increased cell count, increased pressure, or pellicle formation. In cases in which the Nonne or Ross-Jones reaction was questionable this was positive. The author concludes that in all cases with blunted sensorium, convulsions, fever, and evidence of severe infections, lumbar puncture should be performed and the fluid tested for the Pandy reaction. If positive, a diagnosis of tuberculous meningitis can be made with great certainty.

PROPHYLAXIS AND IMMUNITY

Rowand [32] discusses the pathology and etiology of tuberculosis and presents a plan for the investigation of tuberculosis in childhood.

Vaughan [33] describes the sanatorium treatment and prophylaxis of tuberculosis in Detroit.

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30. Alexander, H.: Ztschr. f. Tuberk. u. Heilstättenw. **33**:321 (April) 1921.
31. Widmaier, E.: München. med. Wchnschr. **68**:772 (June 24) 1921.
32. Rowand, A.: Lancet **2**:650 (Sept. 24) 1921.
33. Vaughan, H. F.: Nation's Health **3**:625 (Nov.) 1921.

Fontes [34] gives an historical review and a plan for a general campaign against tuberculosis. He cites the gradual decline in the death rate from tuberculosis and attributes this to acquired immunity from infection early in life. In another article [35] Fontes tabulates a large number of international statistics on the prevalence of tuberculosis, commenting on inherited predisposition and inherited resisting powers. In a third paper [36] he describes "training in hygiene which will enable us to save the child of today and give him resistance for tomorrow." Fontes outlines a plan of campaign as to education, physical culture, and protection.

Jones [37] is of the opinion that from 50 to 100 per cent. of American children have tuberculous infection, and that it is the duty of the schools to find those who are likely to develop clinical tuberculosis and to give them special care. The question is, how to keep these children in school and at the same time to decrease the possibility of eventual tuberculous disease. The first step is to flag the attention of the parents; the next is to secure a complete physical examination of the child and a detailed inquiry into his mode of life. The Pirquet test is important, and the fresh air schoolroom and nutrition class most valuable aids. If the child is reached, the conversion of the parents follows automatically.

Slater [38] points out: "The chance of escaping infection is almost impossible but infection alone will not cause clinical tuberculosis. When clinical disease develops there are present both infection and a lowered resistance, neither of which alone can cause the disease. It is evident that our best means of preventing the disease is to prevent infection and build up a resistance. . . . Every means possible should be exerted to prevent infection during the first year of life. . . ."

Chadwick [39] outlines a plan which will increase the resistance of children to tuberculosis. First, the school system should be made to fit the child and not the child to fit the system. Physically subnormal children should be placed in three groups, according to the degree of physical disability. The first group should contain children only slightly subnormal, who could attend two sessions at school and need only to have their diet changed and more hours of sleep to bring them up to normal. The second group should contain children obviously underweight. They should attend only a half day session and spend the other half day out of doors. Their diet should be carefully regulated and rest must precede each meal in order to develop the appetite, for a

34. Fontes, A.: Brazil-med. **35**:344 (July 2) 1921.
35. Fontes, A.: Brazil-med. **35**:13 (July 23) 1921.
36. Fontes, A.: Brazil-med. **35**:98 (Sept. 3) 1921.
37. Jones, L.: J. Mich. M. S. **20**:234 (June) 1921.
38. Slater, S. A.: Minnesota Med. **4**:650 (Nov.) 1921.
39. Chadwick, H. D.: Am. Rev. Tuberc. **4**: 926 (Feb.) 1921.

tired child will not eat. In the third group should be children with symptoms of active disease. These should go to a sanitarium school with constant supervision. All underweight children who attend the morning session should be provided with a lunch of bread, butter and milk. School nurses are needed to follow up the children in their homes and to see that the parents realize that these children are in need of extra care to prevent the development of serious illness.

Bradley [40] describes the work for the prevention of tuberculosis carried out among children in Pennsylvania. At Mount Alto and Cresson, 465 tuberculous children are cared for and receive definite classroom instruction, as well as hygienic care. One hundred clinics are maintained throughout the State for the treatment of tuberculosis and for the dissemination of knowledge to prevent the spread of disease. A number of open air schools are supported for children who are known to have fever or who suffer from malnutrition.

Peyrer [41] believes that infants with positive tuberculin reactions are a source of danger in hospital wards, even if there are no tubercle bacilli found in the sputum. Older children, often with few clinical findings, occasionally have tubercle bacilli in the sputum and also are a source of infection. As the author thinks that primary infection in children, if acquired outside the family, is especially dangerous, he is particularly careful to avoid hospital infection. He believes that all hospitals should have an observation ward where newly admitted children are kept until tuberculin tests have been made and the sputum examined. After four days, children with a positive tuberculin reaction or with tubercle bacilli in the sputum can be placed in the tuberculosis ward, while others can safely be admitted to the general ward. According to Peyrer, if a child has a positive tuberculin reaction, there is no danger of reinfection.

Chadwick [42] has attempted to solve the question of malnutrition as an etiologic factor in tuberculosis by making a physical examination of underweight children in the schools of Westfield, Massachusetts. In one school of 659 pupils of all ages, he found 186 children suffering from malnutrition. Physical examinations were made of 146 children in this group and of twenty-two in the group of normal children, and 53 per cent. of the 168 gave evidence of tuberculosis of the lymph nodes and of the structures at the root of the lung. In the nine Westfield schools with 2,828 children, 32 per cent. were suffering from malnutrition, and, if the law of averages holds, fully one-third of these children had diseased bronchial nodes, the first step in the development of tuberculosis. The author believes from his study that tuberculosis and malnutrition are closely allied and questions whether malnutrition

40. Bradley, W. N.: Penn. M. J. **24**:285 (Feb.) 1921.
41. Peyrer, K.: Arch. f. Kinderh. **69**:419 (June) 1921.
42. Chadwick, H. D.: Am. Rev. Tuberc. **5**:674 (Oct.) 1921.

may not pave the way for implantation of the tuberculous infection which is present in most children. The evidence collected confirms the belief that antituberculosis activities should be recommended more often in child welfare.

Bernard and Debré [43] emphasize the importance of separating the infant from the tuberculous mother, even if already infected, for it is prolonged, repeated infections that determine a severe tuberculosis in the infant. The authors assert that, if the infant does not die within a month of separation, the disease will probably not prove fatal. In the Laennec Hospital for tuberculous mothers the infants are taken away at once. If, after repeated tuberculin tests, they are found free from tuberculosis, they are placed in private homes. If they are already infected, they are kept under observation to determine the degree of the infection. A child with active tuberculosis is kept in the hospital and the disease usually proves fatal. Infants with a positive cutaneous reaction and symptoms on the part of the gastro-intestinal tract, are given mother's milk and kept in the fresh air until it is proved that the disease is latent; then they are sent either to a crèche or are boarded out in private families.

Köffler [44] has studied the significance of reinfection with the tubercle bacillus. Animal experimentation has taught that a tuberculous infection causes a relative immunity from reinfection with small numbers of bacilli but is no protection against massive infection. On the other hand, animals show a sensitiveness to reinfection with massive doses. Köffler gives tables which show that this is true also in man. His first table shows a number of families, one of whose members has a large number of tubercle bacilli in the sputum. All the children, except those of one family of three, reacted to tuberculin, and all, except two older children, were markedly sensitive to tuberculin. In the second table, illustrating families one of whose members occasionally has tubercle bacilli in the sputum, the children were very slightly sensitive to tuberculin. As to the fate of the children in the two groups, it was found that there was a much higher percentage of severe cases, hence a higher mortality, among the younger children of the first group, but there was practically no difference in the morbidity or mortality among the older children of the two groups. The author believes that reinfection has, then, far less significance than primary infection.

Köffler [45] also reports the results of his investigations on infection among the members of families in which tuberculosis is present. He worked among children from the clinic, the infant welfare and tuber-

43. Bernard, L., and Debré, R.: Paris méd. **11**:27 (Jan. 1) 1921.
44. Köffler, T.: Arch. f. Kinderh. **70**:95 (Oct.) 1921.
45. Köffler, T.: München. med. Wchnschr. **68**:1172 (Sept. 16) 1921.

culosis consultation, dividing them into three groups: Group 1, composed of eight families, one of whose members had numerous tubercle bacilli in the sputum and many moist râles over the lungs. All the children of these families reacted to tuberculin, with the exception of three infants. Group 2, composed of nine families, whose affected member had only a few tubercle bacilli in the sputum; of the twenty-nine children of these families, fourteen were infected. Group 3, families in which some member had clinical tuberculosis but no tubercle bacilli in the sputum. A point of interest was that of the thirteen infants in the three groups only three gave a positive tuberculin reaction and only one of the four infants was in the first group, that which contained a patient having numerous tubercle bacilli in the sputum.

The author draws the following conclusions from his study: A patient expectorating sputum containing tubercle bacilli will infect all the children in the family, but infants under 1 year of age often show no reaction, in spite of every opportunity to become infected. Patients whose sputum contains only a small number of tubercle bacilli are much less infectious. Patients who have no tubercle bacilli in the sputum are not infectious. Patients with grave clinical pulmonary tuberculosis, with occasionally profuse bloody sputum, are exceedingly dangerous to children. Children over 1 year of age are always infected, if there is abundant and long continued opportunity. These children become ill as the result of the first infection and present a high mortality. Young children in families of patients, who have only a few tubercle bacilli in the sputum, do not show such a tendency to acquire tuberculous disease. Children over 2 years of age, though opportunity is given, do not become infected so often as younger children, and the mortality is lower. Children of patients who eliminate large quantities of bacilli are, on account of constant reinfection, highly sensitive to tuberculin.

Stuhl [46] is of the opinion that, if the infant is not taken away from the tuberculous mother, the mother should nurse the child. He thinks the passage of antibodies from mother to infant by the milk has been proved by animal experimentation and that these produce a passive immunity. Daily examples of infants who have escaped infection when nursed by their tuberculous mothers also prove that the milk contains antibodies. The author believes, too, that the number of antibodies in the milk can be increased by treating the mother with tuberculin during pregnancy and lactation.

Cargin [47] laments the lack of control over the milk supply in England. He cites the high incidence of tuberculosis, human and bovine types, and says: "Apart from the infection of the human body with the bovine bacillus, when it is considered that the number of deaths

46. Stuhl, C.: Med. Klin. **17**:315 (March 13) 1921.
47. Cargin, H. M.: Brit. M. J. **2**:894 (Nov. 26) 1921.

from tuberculosis in the first year of life is probably much higher than one in twenty-six (Sir A. Newsholme), and that the total deaths from this disease in England and Wales amounts approximately to 50,000 per annum, it will be agreed that the most stringent regulations are urgently necessary to enable infected and diseased animals to be disposed of without delay."

Blatt,[48] recording observations on the physical development of tuberculous children, takes two groups for the basis of his study: a control group of 614 children who showed no evidence of tuberculosis and whose parents were free from the disease, and a group of 508 children with suspicious or positive evidence of tuberculosis, whose parents were tuberculous. The necessity for a control group of children of the same social status and living in a similar environment was shown by a comparison of the control group with the ideal weights given by the Children's Bureau of the Department of Labor. Blatt's statistics of the initial weight and height show that the weight in the control group reached that of the Children's Bureau standard more frequently than did the weight of the tuberculous group; but the height in the tuberculous group reached that of the Children's Bureau standard before that of the control group. The tuberculous child is the tall, lanky one.

The children of the two groups were observed over a variable period of time. The minimum average period for the boys was fourteen months and the maximum fifty-one and one-half months; for the girls the minimum was nine months and the maximum sixty-nine months. After this period of observation the children in the tuberculous group attained the normal standard of height and weight more frequently than did those of the control group, although the children of neither group reached the standard of the Children's Bureau. The superiority of the children of the tuberculous group over those of the control group Blatt believes due to improvement in sanitation, food, and the removal of defects.

Von Ruck and Flack[49] add another contribution to their previous reports on vaccination of children against tuberculosis. A total of 3,000 children have been vaccinated since 1903, and not a single case is known, according to the authors, in which the tuberculosis recurred or became active. The time intervening since the vaccination has, however, been too short to draw final conclusions. If vaccination is not resorted to during the first years of life, infection is already accomplished. Since in about 70 per cent. of the cases infection had already taken place, the authors cannot regard their work as a strictly prophylactic measure against tuberculosis but one against "consumption." Children in a

48. Blatt, M. L.: The Physical Development of Tuberculous Children, Am. J. Dis. Child. **21**:575 (June) 1921.

49. Von Ruck, K., and Flack, R. E.: M. Rec. **99**:1048 (June 18) 1921.

tuberculous environment should be vaccinated at birth; but every child should be vaccinated, and the earlier it is done the better are the prospects that no tuberculous infection will occur.

Shiga [50] has attempted to immunize children threatened with tuberculosis and to treat early forms. He uses a serovaccine in six different dilutions: from 1:5000 to 1:100. The sixth solution consists of virulent, living tubercle bacilli from 1:20, of which, at first, 0.2 c.c. and then 1.0 c.c. are injected. The author has treated in the last four years 300 ambulatory cases of tuberculosis and has given the vaccine as a protective measure in twenty cases. His results are satisfactory.

Jaenicke [51] believes that the Petruschky percutaneous method of prophylaxis of tuberculosis in children is of value.

Montenegro [52] made four intradermal tests with each of three partial antigens in twenty-four children before and after a three months course at a seashore sanatorium. Along with general improvement in the active group, the reactions were always intensified. He believes that the reaction to the partial antigens of the tubercle bacillus is much more instructive than the reaction to any "whole" tuberculin.

Cozzolino [53] agrees with Peyrer that tuberculous infants are a source of infection even if there are no tubercle bacilli in the sputum. He cites the instance of a tuberculous infant with a negative sputum who infected two older sisters.

Wallgren [54] experimented with rabbits and found that young animals are not less resistant to infection than older animals. He thinks this may be true in the human being also, and that the fact of manifest tuberculosis in infants and young children being rapidly fatal is due to a massive infection. Clinical evidence, therefore, as to the gravity of tuberculosis in infancy does not necessarily indicate that the resistance in infancy is less than in childhood or adult life.

Ickert [55] reports that in 939 homes where tuberculosis was present the contagious member of the family was isolated in the house in 536 instances, away from the house in seventy cases, and in 103 the children were removed from the home.

ETIOLOGY AND PREVALENCE

Krause [56] does not believe that the only mode of tuberculous infection in childhood is direct contact with tuberculous patients. He believes that infection from dried sputum must be seriously considered. Indoors,

50. Shiga, K.: Internat. J. Pub. Health. **2**:34 (Jan.-Feb.) 1921.
51. Jaenicke, C.: Ztschr. f. Tuberk. u. Heilstättenw. **33**:265 (Feb.) 1921.
52. Montenegro, V.: Arch. Espan. de Pediat. **5**:65, 1921.
53. Cozzolino, O.: Pediatria **29**:633 (July 15) 1921.
54. Wallgren, A.: Tubercle **2**:481 (Aug.) 1921.
55. Ickert, F.: Ztschr. f. Tuberk. u. Heilstättenw. **34**:355 (June) 1921.
56. Krause, A. K.: New York State J. Med. **21**:83 (March) 1921.

the sputum bespatters the floor where children are playing. Out of doors, the children engage in ground games and contaminate their hands with the dirt of the sidewalks and streets, containing dried sputum from many persons. There are few children who do not put their fingers in their mouths, thus completing the chain of transmission.

Ribadeau-Dumas [57] believes that tuberculosis in infancy is nearly always the result of inhalation of the tubercle bacillus. The primary lesion is found most frequently at the bases of the lungs and is usually a single tuberculous nodule with miliary tubercles in the neighborhood. If active, there is an area of caseous degeneration, surrounded by a zone of congestion, which sometimes involves the entire lobe of the lung and resembles a pneumonia hepatization. The latent stage is seen in older children when the primary lesion consists of encysted, fibrocaseous tubercles, often calcified. The active process, according to the author's

TABLE 1.—*Children Found to be Infected with Tuberculosis Among Those Subjected to the Pirquet Test*

Age.	1912-1914 (600 Children) Per Cent.	1914-1916 (658 Children) Per Cent.	1916-1918 (638 Children) Per Cent.	1919 (271 Children) Per Cent.	1920 (249 Children) Per Cent.
1 - 3 months	0.0	2.4 (41)	4.7 (43)	0.0 (16)	2.9 (35)
4 -12 months	5.0	7.8	9.4 (85)	17.0 (48)	4.2 (48)
1 - 2 years	12.0	23.0	26.0 (74)	11.0 (35)	17.6 (34)
3 - 4 years	32.0	25.0	52.0 (96)	29.0 (47)	39.2 (28)
5 - 6 years	33.0	50.0	51.5 (66)	57.5 (33)	47.6 (21)
7 -10 years	47.0	56.0	43.5 (163)	47.0 (57)	57.5 (40)
11 -14 years	56.0	66.0	60.0 (111)	63.0 (55)	60.4 (43)

observation, occasionally starts in these old cicatrized areas, but as a rule shows no sign of activity even when the lung is the seat of an active secondary process. From the primary focus the hilum glands become involved, then the apices of the lungs. Apical lesions tend to spread more extensively, and are more serious than the primary hilum lesions.

Van Zwaluwenburg and Grabfield [58] have collected evidence which they believe points to an intimate relation between the occurrence of tubercles in the faucial tonsil and the so-called pleural cap. The pleural cap is a shadow seen in roentgen-ray plates which occurs along the surface of the second rib and is separated from the shadow of the second rib by a clear space from 3 to 4 mm. wide. The study of consecutive sets of plates on the same individual taken at considerable intervals, established certain definite progressive changes in the development of this shadow with the lapse of time. The writers examined with roentgen ray the chests of sixteen persons who had tuberculous lesions in their tonsils. All but one showed the pleural cap. The chests of

57. Ribadeau-Dumas, L.: Les Tuberculosis de l'Enfant et de l'Adulte, Paris, Maloine et fils, 1921, **17.**

58. Van Zwaluwenburg, J. G., and Grabfield, G. P.: Am. Rev. Tuberc. **5:57** (March) 1921.

seventy-seven patients whose extirpated tonsils were found free from tuberculosis were also examined. Three disclosed a pleural cap while twenty-four did not.

Peyrer [59] reports two cases which illustrate the malignant course that tuberculosis may run in older children.

Between January 1918 and October 1920, Sander [60] examined 992 children of the city of Dortmund in order to ascertain whether tuberculous infection had increased since the war. He found that among children aged 2 years, hardly 6 per cent. were affected, and among those from 5 to 6 years of age only 19 per cent., whereas at this age in other cities the average is 90 per cent.

Ickert [61] has collected mortality statistics on tuberculosis in children and youths during the years of the war. He found the mortality increased in Germany and in Holland, in the former ten times more

TABLE 2.—*Percentage of Infected Children Who Exhibited Clinical Tuberculosis, and Percentage of Mortality Among the Latter*

	1912-1914		1914-1916		1916-1918		1919		1920	
Age.	Tuberculosis, per Cent.	Deaths, per Cent.	Tuberculosis, per Cent.	Deaths, per Cent.	Tuberculosis, per Cent.	Deaths, per Cent.	Tuberculosis, per Cent.	Deaths, per Cent.	Tuberculosis, per Cent.	Deaths, per Cent.
1 year.....	100	80	70	77	60	67	75	50	66	50
2 - 4 years..	0.5	21	66	58	54	67	55	40	47	12.5
5 - 6 years.....	0.4	20	35	61	32	45	47	33	70	33
7 -10 years.....	32	7	32	40	29.5	33	41	36	39	44
11 -14 years.....	28	6	27	14	12	10	14	33	15.4	0

than in Holland. This increase did not affect all ages equally. For young children it was 100 per cent., for schoolchildren 50 per cent. and for young adults 200 per cent. During school age, because of specific immunity, there is less danger to life and a greater tendency for the tuberculous process to heal.

Umber [62] presents exact statistical data which concern 2,416 children who were treated at the Municipal Hospital of Charlottenburg, Berlin, during the years from 1912 to 1920. Only those children have been listed as nontuberculous who remained negative to the Pirquet test after repeated application. It will be seen from these figures that, whereas in the years before the war no infants from 1 to 3 months were found to be infected, this was no longer the case after the outbreak of the war.

Examination by Schram [63] of 500 children under 9 years of age from homes where tuberculosis existed showed that 80 per cent. gave a positive tuberculin reaction. Among 168 children in homes where

59. Peyrer, K.: Beitr. z. Klin. d. Tuberk. **47**:164, 1921.
60. Sander: Deutsch. med. Wchnschr. **47**:532 (May 12) 1921.
61. Ickert, F.: Ztschr. f. Tuberk. **34**:7 (April) 1921.
62. Umber, F.: Ztschr. f. Tuberk. **33**:257 (Feb.) 1921.
63. Schram, T.: Norsk. Mag. f. Laegevidensk. **82**:740 (Oct.) 1921.

tuberculosis was particularly contagious, positive reactions were obtained in 100 per cent. of children over 5 years of age. Schram feels that it is impossible to protect children in such homes.

Hempelmann [64] states that: "Infection with the tubercle bacillus usually takes place sometime after birth from exposure to another individual who is suffering from the disease, or from an infected milk supply. . . . The mortality among infants is 78.7 per cent. during the first year of life and 57.4 per cent. between the ages of 1 and 2 years."

Hamburger,[65] in estimating the prevalence of tuberculosis, urges that children in schools and contagious diseases hospitals be selected rather than child patients in dispensaries.

LESIONS

Oldenburg [66] relates that of the 130 children under 4 years of age with pulmonary tuberculosis at the sanitarium in his charge, 53 per cent. were dismissed much improved or cured, and 64 per cent. of the 105, with an interval up to six years, have been in average good health since; 20 per cent. died, and no information could be obtained in regard to 16 per cent.

Zimmermann [67] has made a study of the frequency of severe pulmonary tuberculosis in 333 children, and found that apparently cases of severe pulmonary tuberculosis in children are more frequent than they formerly were. In a previous study, 12 per cent. of the severe cases were fatal, in this study 25 per cent.

Barchetti [68] had under observation for from two to four years fifty-one infants of tuberculous mothers. Of these, fourteen remained free from tuberculosis, thirty-seven showed evidences of the disease. Of the thirty-seven tuberculous infants, eleven were discharged clinically well and twenty-six died. Of the fourteen infants who did not contract the disease, eleven were less than 6 months old and four were in the second half of their first year. Of the eleven patients discharged as clinically well, seven were examined later and gave no evidence of tuberculosis.

Opie and Anderson [69] state that: "The lesions which occur in the lungs of almost all individuals who die from conditions other than tuberculosis have the characteristics of the tuberculosis of childhood, that is, they occur as foci in the substance of the lung and are not more

64. Hempelmann, T. C.: Internat. Clin. **2**:143, 1921.
65. Hamburger, F.: Norsk. Mag. f. Laegevidensk. **82**:294 (April) 1921.
66. Oldenburg, T.: Ugesk. f. Laeger **83**:683 (May 26) 1921.
67. Zimmermann: Ztschr. f. Kinderh. **28**:59 (Feb.) 1921.
68. Barchetti, K.: Monatschr. f. Kinderh. **21**:563 (Sept.) 1921.
69. Opie, E. L., and Anderson, Hans: Am. Rev. Tuberc. **4**:629, 1921.

frequent in the apices than elsewhere. They are accompanied by more extensive lesions in the adjacent lymphatic nodes. The occurrence of these focal lesions, which are almost constantly found, does not exclude the more familiar type of tuberculosis, namely, the apical lesion. In association with the apical lesions, which occur in the later period of childhood and in adult life, there is no caseation nor calcification of the regional lymph nodes. . . . Apical lesions increase in frequency with increasing age." They rarely occurred before 10 years of age; from 10 to 18, the incidence was 11 per cent., between 18 and 50 years of age, the incidence of apical lesions was much increased, for they were present in more than one-third of those who had died from all causes.

Simon [70] has for a number of years turned his attention to the study of the primary forms of tuberculosis in children. He was able to demonstrate the focus in roentgen-ray plates in thirty-six cases. In twenty-four of the cases the lesion was single. In instances of a single lesion the right side was involved three times as often as the left. That the lesions of the left side are not found so frequently is owing to the fact that the cardiac shadow hides a large part of the pulmonary field. Only rarely were the hilum changes limited to the side of the primary focus. Clinical diagnosis of the primary focus is impossible without the roentgen ray. Clinical findings always depend on hilum changes, except in very young children.

Gruber [71] found, in a series of necropsies on twenty-five soldiers (Senegal-African) who died from pulmonary tuberculosis, pulmonary and glandular tuberculous lesions similar to those found in European children. This testifies, Gruber believes, to unpreparedness, the defencelessness of those exposed to infection for the first time, and confirms the fact that tuberculosis in adults is, in the fullest sense of the word, a children's disease.

Alesandrini,[72] on the basis of radiologic examinations, which were controlled by clinical observations and necropsy findings, denies that apical infection in adults is due to a primary infection in childhood. The primary focus is usually in the lower lobes and extends outward from the hilum.

Vis [73] studied the localization of tuberculous lesions in children. He believes that the hilum is the most frequent site of clinical tuberculosis for two reasons. The infant has little or no immunity to the tubercle toxin, and offers only slight resistance to the development of

70. Simon, G.: Ztschr. f. Tuberk. u. Heilstättenw. **34**:345 (June) 1921.
71. Gruber, G. B.: Ztschr. f. Kinderh. **28**:243 (March) 1921.
72. Alesandrini, P.: Policlinico **28**:1 (Jan.) 1921.
73. Vis, W. R.: Apex, Hilum and Lower Lobe Lesions of Tuberculosis in Childhood, J. A. M. A. **76**:1156 (April 23) 1921.

the infection. The lymphatics carry the infection to the nearest lymph gland and then to the other glands in the chain. Thus an early involvement of the hilum is inevitable in most cases. From personal observation and from statistics obtained in the literature, the writer believes that in children apex involvement is more common than lower lobe involvement.

St. Engel [74] has for a number of years studied the so-called epituberculous pulmonary tuberculosis described by Eliasberg and Neuland, and, on the whole, his conception of the disease coincides with that of the latter authors, but he prefers the term paratuberculous infiltration because the infiltration surrounds and is not implanted on the tuberculous focus. The onset in St. Engel's cases was more rapid than it was in the cases described by Eliasberg and Neuland and fever was present. Otherwise, the symptoms were similar. The roentgen ray substantiated the physical findings and showed that the infiltration was not limited by the pulmonary fissure. The disease in St. Engel's cases ran a chronic course, but finally all signs disappeared and the shadows on the roentgen-ray plate gradually cleared from periphery to hilum. This favorable outcome shows that the disease itself is not essentially tuberculosis but possibly pneumonia in the presence of tuberculous infection. Necropsies in three cases confirmed this supposition. Tuberculous changes occurred in the glands but not in the chronic thickened pulmonary tissue, and the infiltration was always on the same side as the tuberculous glands. Gravinghoff [75] believes that the work of Eliasberg and Neuland on epituberculous infiltration is a step forward in the knowledge of chronic pulmonary disease of childhood. He has made a careful study of four cases and concludes that, although the condition is not very common, it should be given further consideration and study. In one of his cases which came to necropsy, Gravinghoff found no evidence of tuberculosis.

Greenberg [76] calls attention to a type of tuberculosis in children which he calls chronic tuberculous hilum pneumonia. He defines it as a diffuse or parenchymatous process involving the portion of the lung immediately adjacent to the hilum, characterized by a gradual onset, comparatively mild constitutional symptoms, and fairly definite physical signs. As a rule, the disease ends in recovery, even in children under 2 years of age.

Eliasberg and Neuland [77] describe in detail gelatinous infiltration of the lungs in children and differentiate it from epituberculosis infiltration.

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74. St. Engel: Berl. klin. Wchnschr. **58**:877, 1921.
75. Gravinghoff: Monatschr. f. Kinderh. **21**:447 (Aug.) 1921.
76. Greenberg, D.: Chronic Tuberculous Hilus Pneumonia in Children, Am. J. Dis. Child. **21**:65 (Jan.) 1921.
77. Eliasberg, H., and Neuland, W.: Jahrb. f. Kinderh. **94**:102, 1921.

The acute onset and the rapid spread of the process over the entire lobe seem to point to rupture of tuberculous material into one of the pulmonary vessels. The onset and the course of the disease differ materially from epituberculous infiltration with its gradual onset and tendency to end in recovery. Three symptoms of gelatinous infiltration are always lacking in epituberculous infiltration, namely, high temperature, involvement of other parts of the lungs, as revealed by the roentgen ray, and the presence of tubercle bacilli in the sputum. The general condition of the children differs greatly in the two conditions.

Siegel [78] describes four cases of pulmonary tuberculosis in young children brought to the hospital with minor complaints, or with a diagnosis other than tuberculosis. He details the differential diagnosis.

Schott [79] describes a very unusual form of pulmonary tuberculosis under the name of "honeycomb" lung. The patient, an 8 months old infant, was brought to the hospital after a few months of paroxysms of coughing and vomiting. Examination showed slightly impaired resonance with faint breath sounds over the lower lobe of the right lung, and a few bronchial râles scattered over the left lung. Later, the impairment over the right lung became more marked. The tuberculin and blood Wassermann reactions were negative. The child died with symptoms of cyanosis and dyspnea. At necropsy there was found a widespread and unusual form of phthisis of the right lung. On section the entire lower lobe and part of the middle lobes were found honeycombed with cavities separated by thickened pulmonary tissue. The cavities varied in size from a pinhead to a bean. Some were filled, others were empty. Blood vessels could be seen, but no bronchi. From the microscopic examination it was determined that the cavities were not the result of a bronchiectasis, but were *ectasis infundibulae,* that is, dilatations of the part of the respiratory tract still partly lined with cylindric epithelium. The walls of the cavities consisted of a thin layer of tuberculous granulation tissue in which were cells of various kinds, epithelial and plasma, a few leukocytes, and typical giant cells containing tubercle bacilli. No explanation was given as to the manner in which these cavities were formed.

Schoenstein [80] reports a case of pneumothorax in an 8 months old infant. The diagnosis was made with the roentgen ray during life. Necropsy revealed a tuberculous cavity which had ruptured into the pleura.

Bourne [81] reports a case of complete pneumothorax in an 18 months old infant. He finds it interesting for two reasons: first, because of the

78. Siegel, A. E.: New York M. J. **114**:223 (Aug. 17) 1921.
79. Schott, A.: Beitr. z. Klin. d. Tuberk. **48**:112, 1921.
80. Schoenstein, E.: Pediatria **29**:535 (June 15) 1921.
81. Bourne, G.: Brit. M. J. **1**:526 (April 9) 1921.

extreme rarity of the condition, and second, because it sheds some light on a probable mode of transmission of the tubercle bacilli to the lungs in childhood. The patient was admitted to the hospital with a temperature of 102 degrees, cyanosis, cough, and dyspnea. He had been well until three months before, when he had an attack of measles, after which there was loss of appetite, constipation, emaciation and cough. The cyanosis had developed only a few days before entrance. Examination of the chest revealed a complete pneumothorax of the left side and a bronchopneumonia of the right lung. The child died, and at necropsy the left lung was found completely collapsed, except at the apex where it was adherent to the pleura. The left parietal pleura was studded with tubercules, as was also the left lung. At the apex of the lung was a cavity which communicated by a small rent with the left pleural cavity; in the right lung were many tubercles. The hilum glands were only slightly enlarged and not caseous. The mesenteric glands, on the other hand, were enlarged and caseated. The liver, spleen and kidneys contained numerous miliary tubercles.

Gloyne [82] says there are three ways in which the tubercle bacilli may reach the bronchomediastinal glands: (1) by direct drainage from the lung parenchyma, bronchioles, and subpleural tissue; (2) by anastomosis between the mediastinal lymphatic vessels and those of the thoracic duct or those of the cervical glands, and (3) by direct blood infection through branches of the pulmonary or bronchial arteries. In order to study further the pathology of mediastinal glands, at necropsy Gloyne dissected out all glands in five tuberculous and three nontuberculous patients. The average number found in the eight cases were: tracheal, nine; interbronchial, thirty-five; bifurcation, five; superior mediastinal, ten. The mediastinal and cervical glands were found microscopically to contain tubercles, although none could be detected by the naked eye. There was not sufficient variation in the severity of the microscopic lesions to demonstrate the course of the tuberculous infection along the chain of mediastinal glands. Roentgenograms of glands showing calcareous nodules were readily distinguishable from those showing anthracosis, caseation, microscopic deposit of tubercle, or malignant disease, by their extreme density and the sharp outline of the shadows produced by calcareous deposit.

Méry [83] also believes it very important to know the manner of dissemination of tuberculosis from the tracheobronchial glands. He says this occurs by means of the circulation, bacillemia, by rupture of the gland into a bronchus, and by direct extension.

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82. Gloyne, S. R.: Tubercle **2**:300 (April) 1921.
83. Méry, H.: Presse méd. **29**:313, 1921.

Frischman [84] calls attention to the well established fact that tracheobronchial tuberculosis follows focal pulmonary infection in childhood, and that lesions in the tracheobronchial glands are larger and more common than pulmonary lesions.

Rüscher [85] has made a study of thirty cases of bronchial asthma in children, with the idea of ascertaining whether there is any relation between this condition and tuberculosis of the bronchial glands. Sixteen of the cases gave a negative and fourteen a positive reaction to tuberculin. Almost all the children showed more or less marked evidence of the so-called exudative diathesis.

Laborderie [86] describes the roentgen-ray picture of enlarged tracheobronchial glands. In concluding his article, the author emphasizes the importance of the roentgen ray not only in the diagnosis but also in the treatment of enlarged tracheobronchial glands.

Thiers [87] studied tuberculous bacillemia in children. Her observations were made on twelve cases of tuberculosis, which included four cases of meningitis, two of Pott's disease, one of acute disseminated tuberculosis, one of tuberculous adenitis, two of ulcerocaseous tuberculosis, one of pleuroperitoneal tuberculosis, and one of ulcerocaseous peritonitis. The blood was obtained from one of the veins in the elbow or from the external jugular vein, treated with acetic acid and a strongly alkaline solution of sodium hypochlorite (antiformin), and injected into guinea-pigs. Positive results were obtained in three cases only, one of acute disseminated tuberculosis and two of Pott's disease. Thiers believes that the search for tubercle bacilli in the blood should always be made on the living child, that the finding of the bacilli after death is of no significance, because there is a necropsy arrest of the organisms in the blood and viscera. Tubercle bacilli are more frequently found in the blood four or five days before death, never forty-eight hours before or on the same day. Bacillemia, then, is evidently a variable and transitory phenomenon, the bacilli appearing in the blood and again disappearing rapidly. This explains the contradictory results of different authors. Negative results show only that the bacilli were not there at the time the search was made, or that the experiment was unsuccessful. They do not show whether they were present before the test or will appear later. Positive results are evidence of a bad prognosis.

Wollstein and Spence [88] report that of 8,919 sick children admitted to the Babies' Hospital in New York, 4 per cent. had symptoms of

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84. Frischman, L.: New York M. J. **114**:634 (Dec. 7) 1921.
85. Rüscher, E.: München. med. Wchnschr. **68**:1155 (Sept. 9) 1921.
86. Laborderie, J.: J. de radiol. et d'electrol. **5**:113 (March) 1921.
87. Thiers, G.: Thésè de Paris, 1921.
88. Wollstein, Martha, and Spence, R. C.: A Study of Tuberculosis in Infants and Young Children, Am. J. Dis. Child. **21**:48 (Jan.) 1921.

tuberculosis in some form. In three cases lesions were found at necropsy that had not been suspected during life. They believe that there is a greater incidence of tuberculosis of infants and young children acquired by inspiring tubercle bacilli than there is of that acquired by swallowing bacilli with food and milk. There is a rapid generalization of tuberculosis in young subjects, the rapidity and degrees of generalization being, as a rule, in inverse proportion to the age. Terminal meningitis is common. There were no cases of healed tuberculosis in 184 necropsies.

Wimmer [89] cites the case of a boy, aged 11 years, healthy except for transient gastric disturbances, who developed acute miliary tuberculosis with delirium and extreme dyspnea. Death occurred in less than two weeks. There had only occasionally been fever during the brief course of the disease, and nothing to explain the dyspnea on auscultation.

Pestalozza [90] examined at necropsy the pancreas in sixty cases of tuberculosis among children. In nine instances there were evidences of tuberculosis, either disseminated miliary tuberculosis or large tuberculous infiltrations. In all the others there were sclerotic changes. The author is of the opinion that connective tissue proliferation is a constant accompaniment of tuberculosis in childhood.

Kleinschmidt [91] has seen few children with phlyctenular conjunctivitis who did not react to repeated Pirquet or intradermal tuberculin tests. He thinks that tuberculosis is a very significant factor in the etiology of this condition, but cannot affirm that it is always the only factor, for even when the children react to a tuberculin test, only a few have tuberculous disease and the others have healed foci. He is inclined to lean toward the teachings of Czerny, who believes that phlyctenular conjunctivitis has an endogenous cause, namely, a constitutional anomaly, the exudative diathesis, and that the exciting cause is some toxin. The tuberculotoxin is the most important, but other toxins, such as those of measles, may play a rôle.

Guillery [92] found that by intravenous injections of tuberculin or by the instillation of tuberculin into the eyes of tuberculous animals, previously treated with tuberculin, he could produce lesions similar to phlyctenules. He obtained the same reaction with staphylococcic toxins. Guillery believes that this shows that phlyctenular disease is a nonbacillary tuberculid, caused by the action of the toxins.

Barney [93] believes that cases of genital tuberculosis in children are often overlooked, or ascribed to an infection by organisms other than

89. Wimmer, L. K.: Semana med. **28**:426, 1921.
90. Pestalozza, C.: Clin. pediat. Modena **2**:261, 1920.
91. Kleinschmidt, H.: Beitr. z. Klin. d. Tuberk. **48**:188, 1921.
92. Guillery: München. med. Wchnschr. **68**:201 (Feb. 18) 1921.
93. Barney, J. D.: Genital Tuberculosis in Male Children, Am. J. Dis. Child. **22**:565 (Dec.) 1921.

the tubercle bacillus. He analyzed eleven cases, the total found in the records of the Massachusetts General Hospital from 1872 to July 1921. The epididymis was affected in all the cases, but bilateral infection was found less commonly than among adults. It occurred in only one case at the time of the patient's entrance to the hospital. In another, the second side became involved twenty-seven months after the removal of the epididymis first affected, in a third case three months after removal. In the other eight patients the disease occurred equally on the right and left sides.

Tuberculosis of other parts of the genital region was found less frequently in children than in adults. In only one of the eleven cases were the kidneys affected. The primary focus of genital tuberculosis can usually be demonstrated by the roentgen ray in the lung or in the bronchial nodes. In the author's eleven cases there was evidence of pulmonary tuberculosis in five cases, of tuberculous peritonitis in two, of tuberculous otitis in two, of bone tuberculosis in two, and of cervical adenitis in one.

Zerbino [94] cites a case of tuberculous orchitis and epididymitis in a boy, aged 5 years, following trauma of the region. The tuberculous process had apparently healed after several months of heliotherapy, but flared up anew during an attack of measles and apparently subsided again. Zerbino calls attention to this temporarily mild form of genital tuberculosis in children and the danger of an exacerbation during puberty.

Curchod [95] describes Hutinel's disease (tuberculous cardiohepatic cirrhosis), and reports three cases, two in children. In early childhood the onset of the disease is usually with bronchitis or pleurisy. In the course of months enlargement of the liver, ascites, and disturbances in the general circulation develop. Examination of the heart fails to disclose a pericarditis or any lesion sufficiently severe to explain the evidences of decomposition. The chief sign is the immobility of the apex, which is adherent to the chest wall. The edema is characteristic in that it begins first in the face, then in the hands and feet. At necropsy cirrhosis of the liver, tuberculous pericarditis, pleurisy, adhesive mediastinitis, and subphrenic peritonitis are found.

In the last few years Hutinel and Merklen [96] have encountered more than twenty cases of tuberculous meningitis in children suffering from hereditary syphilis. They think that syphilis favors the location of tuberculosis in the meninges. Among 206 patients with tuberculous meningitis there were twenty-three with manifestations of syphilis, and

94. Zerbino, V.: Arch. latino-am. de pediat. **15**:317, 1921.
95. Curchod, H.: Rev. méd. de la Suisse Rom. **41**:648 (Oct.) 1921.
96. Hutinel, V., and Merklen, P.: Arch. de méd. d'enf. **24**:521 (Sept.) 1921.

these figures were below the actual, for in those first observed a Wassermann test was not always made. The authors emphasize the fact that, if cases of tuberculous meningitis were studied more carefully as to previous history, clinical, and serologic findings, syphilis would be found more often than it is. There is only one pathognomonic sign of tuberculous meningitis, namely, the presence of tubercle bacilli in the spinal fluid, and these are not easily demonstrated. Because of this difficulty and because of similarity in the two conditions, treatment for syphilis is instituted in all the writers' cases of suspected tuberculous meningitis. If this is not done, there is a possibility of allowing a curable condition to go untreated.

Regan and Cheney [97] observed a case of tuberculous meningitis in a 5-months-old infant, from whom it was impossible to obtain fluid by lumbar puncture. At necropsy this was found to be due to a diffuse infiltration of the pia-arachnoid membrane from the cervical to the lumbar region, with numerous tuberculous granulations which produced marked thickening of the membrane and caused adhesions between it and the dura, almost completely obliterating the subarachnoid space.

Riser and Roques [98] report that in three cases of tuberculous meningitis the preponderance of polymorphonuclear cells in the spinal fluid and the clinical signs of acute meningitis lead to a diagnosis of cerebrospinal meningitis. At necropsy, the meninges showed acute inflammatory changes, although in two of the cases tubercle bacilli were found in the polymorphonuclear cells of the spinal fluid and in the third there was a polyvisceral tuberculosis. The authors believe that the meningeal infection was due to the tuberculotoxins liberated, not on one but on repeated occasions.

Cantilena [99] reports a case of encephalitis with tuberculous meningitis in a 7-year-old child. While in school the child developed a right-sided paralysis without loss of consciousness. The next day there was vomiting, a temperature of 38.6 C. (101.43), and somnolence. Examination showed a convergent strabismus, an up and down movement of the eyeballs, reaction of the pupils to light, but not in accommodation, paresis of the right side of the face and tongue and of the right upper and lower extremity. There was no stiffness of the neck at this time. The cerebrospinal fluid was negative, as was also the blood Wassermann reaction.

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97. Regan, J. C., and Cheney, G. W. H.: A Case of Tuberculous Meningitis with Dry Spinal Subarachnoid Space Due to Diffuse Tubercle Infiltration of the Spinal Meninges, Am. J. Dis. Child. **22**:516 (Nov.) 1921.

98. Riser, and Roques: Ann. de méd. **10**:10 (July) 1921.

99. Cantilena, A.: Riforma med. **37**:458 (May 14) 1921.

On the sixteenth day of illness stiffness of the neck, mydriases, and ptosis developed. The spinal fluid gave a positive Wassermann reaction. Death occurred after forty-six days. Necropsy revealed chronic subacute and acute general miliary tuberculosis. The entire right side of the cerebellum was covered with an area of yellow softening, an encephalitis due to the emboli from the ulcerated gland. Extension of the processes along the cranial nerves and the pyramidal nerve tracts accounted for the paralysis of the eyes and extremities. A later dissemination caused the meningitis and fatal miliary disease.

Slesinger [100] studied an unusual case of abdominal tuberculosis in a 5-months-old baby, who was admitted to the hospital with a diagnosis of probable tuberculous peritonitis. Laparotomy was performed and the abdominal cavity was found to contain intestinal contents and pus from a mesenteric abscess. The child died and necropsy revealed an extensive tuberculous ulceration of the intestines with perforation of one of the ulcers. The mesenteric abscess was in relation to a ruptured tuberculous, caseating gland.

According to Pitts,[101] the belief has been gaining ground that in childhood the intestine may be the primary site of the tuberculous infection, even of the pulmonary type. Pitts reports two cases, one, a miliary tuberculosis in a girl, aged 11 years, and the other, tuberculous meningitis in a 2-year-old boy, in whom a localized tuberculosis of the intestine was apparently the primary lesion. In the first case necropsy revealed in the lower part of the jejunum a number of tubercles, pinhead in size, in and below the mucosa and in the mesentery. Those in the mucosa had not led to ulceration, and the mucous membrane above the tubercles was intact. In the mesenteric, perigastric, and pancreatic lymph glands were tuberculous nodules. In the second case there was a small superficial tuberculous ulcer in the lower part of the jejunum. The mesenteric glands were enlarged and caseous. The cases were of interest not only because the intestine was evidently the portal of entry of the tubercle bacilli, but also because the lesions did not occur in the ileum, where the intestine is richest in lymphoid tissue. The first case showed also that tubercle bacilli can pass into the mucosa without causing superficial injury.

Wrechers [102] had under observation an unusual case of edema, associated with severe intestinal tuberculosis, in a 5-year-old girl. For a few weeks there had been diarrhea and swelling of the ankles and legs. Then the swelling had spread to all parts of the body. On entrance to the hospital the eyes could hardly be opened and examination

100. Slesinger, E. G.: Brit. M. J. **1**:703 (May 14) 1921.
101. Pitts, H. H.: Canad. M. A. J. **11**:740 (Oct.) 1921.
102. Wrechers, A.: Arch. f. Kinderh. **69**:450, 1921.

of the retina showed swelling of the papillae, more marked on the right side. In both lungs were moist râles; over the left upper lobe fine, crackling râles, and impaired reasonance. The urinalysis and the Pirquet tests were negative. On the eighth day in the hospital the child had a convulsion, followed by difficulty in swallowing and paresis of the left arm. The edema of the left arm and leg was very marked. The diarrhea increased, and the general condition became worse. Death occurred on the sixteenth day. Necropsy showed a solitary tubercle of the cerebellum, hydrocephalus, sinus thrombosis, caseous pneumonia in the left upper lobe, and a few miliary tubercles scattered throughout the lungs, tuberculous pleuritis and peritonitis, and a widespread ulcerative tuberculosis of the small and large intestines.

Frenkel[103] reports two cases of spontaneous gangrene of the extremities in the course of tuberculosis. The first was in a child, aged 2 years, who entered the hospital June 21, 1916, because of edema and cyanosis of the lower extremities which had begun three days before. Examination disclosed that the lower extremities were slightly swollen and of a bluish color, very marked in the toes, which looked as if ink had been poured over them. The discoloration gradually merged into the color of normal skin in the middle of the back of the foot, without any line of demarcation. Pin point hemorrhages occurred in the affected areas. The child was suffering also from pulmonary tuberculosis and hemorrhagic nephritis. The general condition became worse and the child died a month after entrance to the hospital. The second case was that of a boy, aged 5 years. On entrance to the hospital, widespread pulmonary tuberculosis and gangrene of the left leg were observed. Swelling and cyanosis had reached the middle of the calf, but the line of demarcation was at the lower third. The tips of the toes were dry and hard. Death occurred shortly after entrance. At necropsy there was found, besides the widespread tuberculous changes in the lung, a thrombus in the left popliteal artery. Microscopically, the vessel wall showed the picture of a toxic arteritis. The author concludes that obliterative arteritis can be caused by tuberculosis as well as by measles, scarlet fever, diphtheria, pneumonia and other infections. He believes, however, that there must be another factor besides the tuberculous infection or it would be difficult to explain the rarity of this complication of tuberculosis.

Marfan[104] believes that the term "scrofula" should be retained because it represents a pathologic condition occurring in tuberculous individuals. Scrofula is seen, usually, in young children only, and is characterized by chronic cervical adenitis and inflammations of the

103. Frenkel, H.: Ztschr. f. Kinderh. **29**:213 (June) 1921.
104. Marfan, A. B.: Paris méd. **34**:13, 1921.

mucous membrane which tends to ulcerate. A very marked tuberculin test is always present even if there are no demonstrable lesions. The tuberculous lesions in scrofula are characterized by their relative benignity and by their ability to confer a certain degree of resistance to the individual.

Ernberg [105] reviews eighty-six cases of erythema nodosum in children and is convinced that this is a manifestation of an anaphylactic process in the course of tuberculosis. He found that the lesions appear in a comparatively early stage of tuberculosis, accompanied by fever, pain in the joints, sometimes marked pallor, pain in the abdomen, and albuminuria. The tuberculous lesions were usually in the bronchial glands and were discovered only by roentgen ray. When the erythema appeared during a late stage, there occurred, in a number of cases, pulmonary symptoms, due evidently to an acute process in the glands. But in nearly all instances, manifestations of active tuberculosis developed after the erythema had run its course. Sometimes this was a generalized tuberculosis. As a rule, all the children reacted positively to tuberculin, even the younger ones, in whom a positive reaction is not the rule.

That the erythema nodosum is an anaphylactic process was shown by the histologic examination of the lesion which was similar to the one produced by the infection of tuberculosis, by the general and local reaction which accompanies the appearance of the eruption, and by the similarity of the entire process to other well known anaphylactic reactions.

Dietl [106] describes a case of tuberculosis of the skin in an infant, aged 19 months, due to infection of an impetigo lesion with tubercle bacilli. When the child was brought for examination, there were typical lesions of impetigo on the dorsum of each foot. On the back was an oval ulcer, 1.5 by 2 cm., partly covered by a scab with the edges infiltrated. The glands in the axilla were the size of a hen's egg; the lungs were normal. The Pirquet test, which had been negative eight weeks before, was now strongly positive. Three months later the child had developed phlyctenular conjunctivitis. The impetigo on the feet had disappeared but the ulcer on the back was still present. It was excised and on microscopic examination proved to be tuberculous. The author believes that the child contracted impetigo and infected the lesion by rubbing tuberculous material into it.

Stillians [107] reports a case of tuberculosis verrucosa cutis, associated with lupus vulgaris and lichen scrofulosorum in a boy, aged 10 years. On the back of the four small toes of the left foot was a warty tumor.

105. Ernberg, H.: Jahrb. f. Kinderh. **95**:1, 1921.
106. Dietl, K.: Monatschr. f. Kinderh. **22**:27 (Oct.) 1921.
107. Stillians, A. W.: Internat. Clin. **2**:32, 1921.

1½ inches (4 cm.) in length and breadth, and ¼ (6 mm.) inch in height, covered with papillary projections; some dark brownish red, others covered with thick, horny, light brown crusts. On the external, anterior surface of the left instep was a second lesion, in part like the one on the toes and partly covered with a thin crust, on removing which a brownish-red erosion remained. Just above the ankle on the external and posterior surface of the leg was a brownish-red, weeping erosion, 3 inches (7.6 cm.) in diameter. Above this was a little larger patch of similar nature. The patient was treated with roentgen ray and soon after a papular eruption appeared, first on the chest, then on the abdomen, arms, and upper thighs. These papules became acuminate and capped by a tiny scale. They were dull red, from 1/16 to ⅛ inch (from 1.5 to 3 mm.) in diameter. The author believes that, without doubt, he was dealing with a group of tuberculous skin lesions; tuberculosis verrucosa cutis on the feet, a superficial type of lupus vulgaris on the leg, and lichen scrofulosorum on the chest, abdomen and arms.

Low [108] describes the various forms of tuberculosis of the skin. Of all these the one which most concerns the general practitioner is lupus vulgaris, when it occurs in multiple lesions. Numerous small red spots suddenly appear scattered over the face, body, and limbs, which show on pressure the apple-jelly like nodules of tuberculosis. This form is found more often in children and adolescents, and often follows one of the exanthems, especially measles. It is embolic in origin and is an evidence of an active tuberculosis somewhere in the body. Another group of tuberculous skin lesions, which are very important, are the tuberculids, namely, lichen scrofulosorum, papulonecrotic tuberculids, sarcoids, and erythema induratum. Lichen scrofulosorum appears in small papules often on the sides of the chest. The papules are arranged in groups; at first pink, surmounted by a minute scale, and in a few weeks becoming brown. If the eruption is very acute, there may be small vesicles or pustules, instead of papules.

The papulonecrotic tuberculid consists of slightly larger lesions than lichen scrofulosorum. These appear as bluish-red papules, the centers of which undergo first a process of necrosis, then crust over, and slowly heal. Crops of eruption appear from time to time.

Erythema induratum scrofulosorum is the best known of the tuberculids. It occurs as rounded or oval bluish-red swellings, frequently on the lower part of the back of the legs. If these swellings break down and ulcerate, their appearance is similar to broken down gummas. After healing, a scar remains, often surrounded by a pigmented area. Another tuberculid is that described by Broch as a sarcoid. It is found

108. Low, R. C.: Edinburgh M. J. **29**:114, 1920.

as single or multiple hemispherical purple elevations of the skin, and usually located on the face or upper extremities.

The treatment of these forms of tuberculosis of the skin is not altogether satisfactory. With rest and general treatment, as for all forms of tuberculosis, most of them, especially the small lesions, disappear. For the larger lesions, such as erythema induratum, the roentgen rays are useful.

DIAGNOSIS

Güterboch [109] is certain that with increasing age, the number of children infected with tuberculosis grows, so that at the age of puberty about one-half are tuberculous. In most instances, infection takes place after birth, but intra-uterine acquired tuberculosis is more common than is usually supposed, because women with a latent tuberculosis can suffer from placental tuberculosis and infect the fetus. The author's experience coincides with that of other writers who find the younger children of the family more frequently the victims than the older. Hilum involvement seems to be the most common form of tuberculosis in children. When the process extends beyond the hilum into the pulmonary parenchyma, the outcome is usually fatal. Apical involvement, however, is not uncommon in children over 5 years of age. The disease apparently runs a similar course in members of the same family, even when there is no family history of the disease.

Pollitzer [110] always found a tuberculous process in the lungs or hilum glands with the roentgen ray in nonrachitic children who had a positive Chvostek's sign. The sagittal thoracic diameter was greater than normal in 70 per cent. of such children, whereas in rachitic children with a positive Chvostek sign the transverse diameter of the chest was greater than normal in 60 per cent. of the cases. He found also that in tuberculous children with a positive Chvostek sign the distance from jugulum to the symphysis pubis was shorter than normal in 60 per cent. of the cases. Pollitzer believes that demineralization which is common in tuberculosis may be responsible for the over-excitability of the nerves causing Chvostek's sign.

Comby [111] is of the opinion that the so-called "typhobacillose" of Landouzy is only a form of tuberculosis with the tuberculous lesion latent. It is an error to believe that there can be fever of tuberculous origin without a lesion somewhere in the body. In children, this lesion is usually in the bronchial glands and ought to be found by auscultation, by roentgen ray, or by the fluoroscope.

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109. Güterboch, R.: Beitr. z. Klin. d. Tuberk. **43**:297, 1920.

110. Pollitzer, R.: Policlinico **28**:1067 (Aug. 8) 1921.

111. Comby, J.: Bull. et mém. Soc. méd. d. hôp. de Paris **45**:939 (June 24) 1921.

Tronconi [112] believes that Zinda's sign is a very important aid in the diagnosis of tuberculous meningitis. This sign consists of a sudden raising and jerking forward of the shoulders when the head is passively moved to the other side. The shoulder remains in this position and resists all efforts to bring it back until the head is again turned toward the median line. Tronconi never found the sign in healthy children or in children suffering from any disease except tuberculous meningitis. He was, on the other hand, able to obtain it in all children with tuberculous meningitis and in every instance he found the diagnosis confirmed at necropsy.

Richard [113] is of the opinion that children of tuberculous parents are born with attributes which make them an easy prey for the disease. This is true also of children with lymphatic diathesis. To make a diagnosis of a pretuberculous child, it is necessary to take a careful history, including that of frequent coughs and colds. Next in importance is the general examination of the child.

Stewart [114] discusses the value of the various diagnostic methods in pulmonary tuberculosis among children. He bases his conclusions on the study of 300 children between 5 and 14 years of age, and thinks that family and personal history lead but a little way toward a diagnosis. Laboratory investigation is limited to the few instances in which the sputum is available. Physical examination is very valuable, but its results are sometimes indefinite in regard both to the existence of active disease and often to the true nature of the morbid changes found. Of the specific tests the quantitative cutaneous is of the greatest value. Radioscopic examinations are unsatisfactory. No one method, then, except the finding of tubercle bacilli in the sputum, can be depended on to make a final diagnosis of tuberculosis in children; but two methods combined, namely, physical examination associated with the quantitative cutaneous test, are preeminently reliable.

O'Brien and Ames [115] have made a study of the roentgen ray and tuberculosis in children. According to these writers it is commonly accepted that the roentgen ray usually shows structural changes of much greater extent than physical examination would suggest. It has been noted also that the roentgenogram is positive in many cases in which the physical examination is negative. These findings were corroborated in the authors' series of forty-four cases. Fifteen cases were given a negative diagnosis by clinical examination, yet showed structural lung changes consistent with pulmonary tuberculosis. Because of these

112. Tronconi, S.: Pediatria **29**:802 (Sept. 1) 1921.
113. Richard, P.: Arch. de méd. d'enf. **24**:215 (April) 1921.
114. Stewart, S. H.: Tubercle **2**:193 (Feb.) 1921.
115. O'Brien, F. W., and Ames, F. B.: Roentgen Ray and Tuberculosis in Infants and Children, J. A. M. A. **76**:1474 (May 28) 1921.

findings, the authors advocate the more routine use of the roentgen ray, in a way analogous to the tuberculin skin tests.

Méry, Détré and Desmoulins [116] emphasize the importance of confirming a clinical diagnosis of tuberculosis in childhood by roentgen-ray examination. Three stages of hilum tuberculosis are recognized. In the first stage the shadows extend hardly beyond one or two intercostal spaces, and the right shadow is more apparent than the left. These shadows are not diagnostic of tuberculosis but are a manifestation of any respiratory disease. In the second stage the shadows are hazy, and spread out each side of the median shadow like the wings of a butterfly; at times the shadow is unilateral. These shadows indicate an active tuberculosis. In the third stage the shadows of the hilum are clear cut, the ramifications are dark and reinforced by small calcifications, either in groups or scattered; the shadows are more extensive and may reach as high as the clavicle or as low as the diaphragm. Sometimes there are present isolated shadows at the bases, in the lateral portions, or in fact anywhere in the lungs, and those, according to the writers, are of significance and probably represent the primary infection of the tracheobronchial adenopathy.

In order to determine the importance of certain physical signs and roentgen-ray findings as indicators of the degree of infection in the tracheobronchial glands, Balyeat [117] examined 449 children under 16 years of age. Especial significance was placed on D'Espine's sign as an indicator of tracheobronchial adenopathy and the appearance of hilum shadows in the roentgenogram as a means of differentiating tuberculous from nontuberculous glands. Balyeat considers D'Espine's sign positive if the tracheal voice is heard below the seventh cervical vertebra in children under 3 years of age; below the first dorsal in children between 3 and 5 years of age; or below the third dorsal in children over 5 years of age. In 116 of the 449 children there was a positive D'Espine's sign. Practically all patients on whom was elicited a positive D'Espine's sign or from whom a history of contact was obtained were roentgenographed. The author believes that only by means of roentgenograms can a tuberculous hilum be differentiated from one that is nontuberculous.

Dunn and Cohen,[118] discussing the diagnosis and the prognosis of tuberculosis in infancy, base their conclusions on a series of 374 cases, in which a clinical diagnosis of tuberculosis was made, and on a series of 138 necropsies, in which lesions of tuberculosis were found. They

116. Méry, H.; Détré, G., and Desmoulins, A.: Presse méd. **29**:221 (March 19) 1921.

117. Balyeat, R. M.: Diagnosis and Significance of Tracheobronchial Adenopathy, J. A. M. A. **76**:988 (April 9) 1921.

118. Dunn, C. H., and Cohen, S. A.: The Diagnosis and Prognosis of Tuberculosis in Infancy, Am. J. Dis. Child. **21**:187 (Feb.) 1921.

believe that special methods of diagnosis are needed for the recognition of the primary focus in the lung, and adopt the following routine measures: The lungs are examined not only for signs of consolidations but also for signs of enlargement of the tracheobronchial lymph nodes. The signs especially looked for are interscapular dulness, prolongation downward of the normal cervical dulness, and D'Espine's sign. The Pirquet cutaneous reaction is made and repeated at intervals, and in suspicious cases a roentgenogram of the chest is taken. If the Pirquet reaction is positive or even suspicious, or if the roentgenograms show the shadow characteristic of tracheobronchial node enlargement, a diagnosis of tuberculosis, primary in the lung, may be made with a fair degree of certainty. If the sole evidence is a positive D'Espine's sign of interscapular dulness, the diagnosis may be made with only a slight degree of probability. In cases in which all three of these forms of evidence are absent, tuberculosis in the primary stage should not be diagnosed. The secondary stage, except in cases of tuberculous bronchopneumonia and general miliary tuberculosis, offers no difficulty in diagnosis. In the majority of cases showing pulmonary consolidation, in which either the Pirquet reaction or the roentgen-ray plate is positive, the correct diagnosis is tuberculous bronchopneumonia.

Debré [119] takes the position that we should always suspect tuberculosis in an infant if another member of the family has it; in fact, many go so far as to consider these infants as positively having tuberculosis. The tuberculin test is of great help when positive, but if negative it should be repeated after several months, for it must be remembered that it takes several months for the organism to develop susceptibility to tuberculin.

Vienna is a city in which tuberculosis has always been widespread, and the war conditions there made it possible for Pirquet [120] to study the pathogenesis and the control of that disease even more closely than before. He states that infection with the tubercle bacillus is pulmonary in 90 per cent. of all cases, and is called "bronchogenetic." The "enterogenetic" form, affecting the intestines, is not so common where milk is usually boiled, but is found more often in countries like the United States and England, where this is not done. The "stomatogenetic" and the "dermatogenetic" forms are very unusual, and one almost never sees the "placentogenetic" form, for the infant usually dies very soon after birth. Tuberculosis, like syphilis, has a primary, secondary, and a tertiary stage. The older and stronger a child, the better it can, while in the first stage, develop a resistance which consists either of greater sensibility or greater immunity, depending on the kind of anti-

119. Debré, R.: Médecine **2**:626 (May) 1921.
120. Pirquet, C.: Policlinico **28**:551, 1921.

bodies formed. The less the child's organism can accomplish this, the sooner it enters the second stage, the dissemination of the germs to all parts of the body. Toward the end of childhood, there appears a development that seems to have some connection with puberty and takes the form of a cavernous destruction of the apex of the lungs. This has been called the third stage, although it may be more a tendency of the tissues, due to the age of the subject, than a true development of the disease.

PROGNOSIS

Debré, Paraf and Dautrebande [121] believe that the prognosis of tuberculosis in infants can be determined by the length of time between infection and the appearance of a positive tuberculin reaction, namely, the antiallergic period. This can usually be ascertained by a series of cutaneous tests at regular intervals, begun as soon as it is known an infant has come in contact with a tuberculous person. Clinical facts and animal experimentation have shown that infection with massive doses of tubercle bacilli causes a short antiallergic period, whereas small doses produce a long antiallergic period. A short antiallergic period, therefore, always means a massive infection, which is followed by a fatal tuberculosis, and a long antiallergic period signifies an infection with few bacilli and a benign course.

Nobel [122] reports his conclusions with regard to the prognosis of pleuritis in childhood. In all, seventy-eight children were observed, and in the entire series tuberculosis was the only etiologic factor found. Thirteen of the children died, twenty-six could not be reexamined after they had left the hospital, and thirty-nine were kept under observation from a period of a few months to nineteen years. In 41.1 per cent. of these, recovery was complete, in 38.4 per cent. there were only slight changes on physical and roentgenologic examination referable to the previous pleurisy, in 10.2 per cent. there were more or less severe changes, such as retraction of the affected side, displacement of the heart, scoliosis, and marked pulmonary infiltration. Therefore, he believes that the prognosis of tuberculous pleurisy is quite favorable.

Harbitz [123] cites cases of tuberculous meningitis which have ended in recovery, and reports necropsies in which healed tubercles have been found. From his observations, Harbitz concludes that tuberculous meningitis may heal, even when there are extensive lesions with exudate and tubercle formation. This curable form occurs largely in persons who have suffered from chronic and relatively benign forms of

121. Debré, R.; Paraf, J., and Dautrebande, L.: Ann. de méd. **9**:443 (June) 1921.

122. Nobel, E.: Wien. klin. Wchnschr. **34**:423 (Sept. 1) 1921.

123. Harbitz, F.: Am. J. M. Sc. **161**:212 (Feb.) 1921.

tuberculosis. It is probable, however, that a more important factor is the resistance of the body which increases with the age of the patient. This is borne out by the fact that, whereas about 60 per cent. of all cases of tuberculous meningitis occur in the first two years of life and quite regularly result in death, recovery has occurred among older children and adults.

Debré and Bernard [124] report a case of tuberculosis in an infant which illustrates the fact that the disease is not invariably fatal at this time of life, and that a long antiallergic period means a benign course. The child was removed from the tuberculous mother on the forty-ninth day of life, and did not give a positive cutaneous reaction until 2½ months old. At that time there were also clinical evidences of infection. Roentgen-ray examination revealed a shadow in the sixth interspace on the right side. In two or three weeks all symptoms subsided and only a latent tuberculosis remained, as revealed by the roentgen ray and positive tuberculin reaction.

TREATMENT

Broca [125] calls attention to the favorable influence of the roentgen ray on tuberculous adenitis. He is very conservative in regard to the total extirpation of the glands. Nevertheless, he finds it valuable in the hands of experienced surgeons in cases of fistulas, which have resisted heliotherapy and roentgen-ray treatment.

D'Oelsnitz and Carcopino [126] report a case of tracheobronchial adenopathy causing symptoms of suffocation, which was successfully treated by roentgen ray. The patient was a 3-year-old child, who suddenly awakened one night with a cry of suffocation. On entrance to the hospital there was slight cyanosis, dyspnea and substernal retraction. The respiratory murmur was diminished on the right side. Roentgen-ray examination showed shadows of enlarged hilum glands, especially on the right side. Immediate amelioration of the dyspnea and retraction of the chest followed treatment with the roentgen ray. From the study of this and other cases the writers believe that a severe congestion of inflammatory reaction in the tuberculous glands caused the symptoms of suffocation and on these reactions the roentgen ray has a very rapid action. They are also of the opinion that the roentgen ray can cause retrogression of chronically enlarged mediastinal glands and can prevent these acute exacerbations. While preparing this article, the authors had occasion to observe a similar case in a 2-year-old child, whose condition also yielded to roentgen-ray therapy.

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124. Debré, R., and Bernard, L.: Bull. et mém. Soc. méd. d. hôp. de Paris **44**:1658 (Dec. 31) 1921.

125. Broca, A.: Progrès. méd. **36**:227 (May 21) 1921.

126. D'Oelsnitz, M., and Carcopino, M.: Bull. et mém. Soc. méd. d. hôp. de Paris **45**:297 (March 4) 1921.

Hubeny [127] states that in recent years the more general application of the roentgen ray for tuberculous adenitis has proved its worth beyond a doubt. The results obtained by roentgen-ray therapy are so uniformly good that it can be safely recommended as the most useful method of treatment. The roentgen ray, in producing healing of tuberculous glands, causes actual destruction of the tuberculous granulation tissue.

Boggs [128] has found in the treatment of tuberculous adenitis that better results are obtained from the use of radium and roentgen ray than from any other method. Radiotherapy alone will cure over 90 per cent. of the cases. Surgeons of experience do not operate primarily for tuberculous adenitis. If they operate, it is only to remove fibrous nodes, after the tuberculous foci have been destroyed by the roentgen ray.

Mulier [129] treated thirty cases of glandular tuberculosis, fourteen of pleuritis, and twenty-two of exudative and adhesive peritonitis with rays from the quartz lamp. The favorable effect was first noticed in the general condition, then followed improvement of the tuberculous focus. Usually from forty to fifty treatments were necessary before complete cure was effective.

Oldenburg [130] publishes the results of sanatorium treatment of 120 children under 4 years of age with pulmonary tuberculosis. Of thirty-seven children below 2 years twenty-five were cured, two improved, and ten died. Of eighty-three children between 2 and 4 years of age, thirty-seven were cured, thirty-one improved, five did not improve, two became worse, and eight died. Later results were studied in 105 children, 64 per cent. remained well six years, 20 per cent. died within the six years, and no information could be obtained regarding the remaining 16 per cent.

Achard [131] does not agree with the general opinion that latent tuberculosis in childhood requires only hygienic, dietetic, and climatic treatment. These must not be neglected but often the administration of tonics is indicated. Iron, arsenic, and manganese are the best drugs to increase the amount of hemoglobin and the number of red blood cells. Beside a suitable diet, it is well to supply an excess of fat, the best form of which is cod liver oil. He feels that children who have been infected with the tubercle bacillus require specific immunization. Old tuberculin is not very satisfactory, since it does not contain all the reactive corpuscular substances of the tubercle bacillus, but there are three preparations which are very satisfactory, Much's partial antigens,

127. Hubeny, M. J.: Internat Clin. **1**:110, 1921.
128. Boggs, R. H.: Am. J. M. Sc. **162**:90 (July) 1921.
129. Mulier, A.: Pedjatria Polska **1**:2, 1921.
130. Oldenburg, T.: Ugesk. f. Laeger. **83**:683 (May 26) 1921.
131. Achard, H. J.: Am. Rev. Tuberc. **5**:405 (July) 1921.

von Ruck's vaccine, and Crofton's (Dublin) antigen. These preparations can bring about complete immunization. Achard believes that deliberate and extensive immunization against the tubercle bacilli would go far toward reducing the morbidity of tuberculosis among adolescents and adults, in ten, twenty or thirty years from now.

After six and a half years of experience, Hyde and Grasse [132] are convinced that much better results can be obtained in cases of surgical tuberculosis, if the disease is not regarded as purely surgical. This type of the disease is a general constitutional one with local manifestation. The authors combine surgery with heliotherapy. Favorable progress is in direct proportion to the intensity of the pigmentation. The most striking local result in the treatment of joint tuberculosis by heliotherapy, and one of greatest importance in early cases, is the preservation of motion in the affected joints. The sun acts as an agent of repair on bone tissue. The effect on sinuses and ulcers is one of marked reaction, and on lymph nodes a reduction in size and absorption of broken down tissue. The effect on effusion in joints, peritoneal and pleural cavities is one of absorption.

The method of alimentary therapy developed by Pirquet [133] has given excellent results after the failure of every medical form of treatment, including tuberculin therapy. His theory is that the formation of antituberculosis antibodies is related to a rich metabolism, and that the whole value of climate in the treatment of tuberculosis lies in finding a climate that excites the patient's appetite and in satisfying it. The nutritional prescription is made out according to the "Nem" system. When no restrictions are necessary, the diet is very simple. Meat is given once a week, the rest of the time milk, starches, potatoes, green vegetables, and fats, a diet easily combined with that of a family. This method of treatment has given excellent results with 100 children under observation; every other form of therapy was gradually abandoned.

König [134] warns against trusting too blindly to conservative treatment of bone, joint, and glandular tuberculous processes outside of well equipped institutions, saying that the results reported by Bier are experimental, as the ultimate outcome is not yet known. König has investigated 1,932 resections reported from twenty sources, five, ten, twenty, or more years ago, and has found that although these were the gravest kinds of tuberculous processes, 68 per cent. have been permanently cured to date.

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132. Hyde, C. L., and Grasse, H.: Am. Rev. Tuberc. **5**:159 (April) 1921.
133. Pirquet, C.: Policlinico **28**:551, 1921.
134. König, F.: München. med. Wchnschr. **68**:642 (May 27) 1921.

Harms [135] reports his experience with artificial pneumothorax in the treatment of tuberculosis of childhood. He has used this method with thirty-seven children, two in the second stage of hilum tuberculosis, and thirty-five in the third. In seven it was impossible to fill the pleura because of adhesions. Five of the children were cured after from twelve to forty-eight months' treatment, four died during treatment, and eleven after the course of treatment was finished. Two children were still under treatment at the time of his report and eight had passed from observation. Harms thinks the treatment should not be undertaken with children under 18 months of age. The technic is the same as that used in adults.

Cole [136] details the surgical treatment of tuberculosis in children.

Homuth [137] had in his care a child in whom an acute ileus was the first symptom of mesenteric tuberculosis. The patient was a 13-year-old school girl who had never had any gastro-intestinal disturbance. Three days before admission to the hospital she developed symptoms of intestinal obstruction with vomiting. When admitted, the child was pulseless, the abdomen being markedly distended, and there was constant vomiting. Operation was immediately performed and the mesentery was found firmly adherent to the intestine. In the mesentery were large, cheesy, tuberculous glands. As it was impossible to free the adhesions, a resection was performed and the patient recovered.

Lefert [138] emphasized the danger of removing the fluid in cases of ascitic tuberculous peritonitis. The exudate contains antibodies needed to combat the disease. If the fluid is removed by puncture, it should be reinjected subcutaneously.

The fact that local surgical tuberculous lesions are metastatic in origin lead Klare [139] to look for pulmonary lesions with the roentgen ray in children suffering from surgical tuberculosis. In most instances pulmonary and bronchial gland lesions were found, and the author emphasizes the importance of treating surgical tuberculosis as a general disease and not limiting it to the local condition.

In discussing the surgical aspects of abdominal tuberculosis, Ladd [140] says that the variety of types of manifestations has led to confusion in its treatment, but there is sufficient data at hand to warrant the establishment of more uniformity of management than at present exists. First in importance should be placed proper hygiene, diet, and outdoor life. Surgery as an aid in selected cases is of unquestionable value, but the

135. Harms: Aerztl. Rundschau, München. **30**:333, 1920.
136. Cole, W. H.: Minnesota Med. **4**:228 (April) 1921.
137. Homuth, O.: Deutsch. med. Wchnschr. **47**:777 (July 7) 1921.
138. Lefert, M. V.: Arch. Espan. de Pediatria **5**:449, 1921.
139. Klare, K.: Beitr. z. Klin. de Tuberk. **46**:183, 1921.
140. Ladd, W. E.: Boston M. & S. J. **185**:317 (Sept. 15) 1921.

cases should be logically chosen as far as difficulties of diagnosis make it possible. If the diagnosis can be made in the stage of localized mesenteric adenitis, excision of the glands is logical, successful, and probably prevents the development of the other stages. If caseous glands are found on operation, when an erroneous diagnosis of appendicitis has been made, they should be removed. If a large single mesenteric abscess is found, it should be incised, the pus evacuated, the cavity wiped out with iodin, and the abdomen closed without drainage. In the ascitic stage laparotomy with evacuation of the fluid is recommended when the patient fails to respond to medical treatment after a reasonable length of time. In the plastic stage, the prognosis is poor with any treatment and operation is resorted to only to relieve the intestinal obstruction, and in this it has occasionally been successful.

Mixter [141] also discusses the surgical aspect of abdominal tuberculosis in children. He believes the indication for operation in tuberculous mesenteric adenitis is clearly defined. There is a localized process which is potentially capable of causing a disseminated peritoneal infection or an acute miliary process. As elsewhere, it should be removed if possible. Operation should be advised in the ascitic form only when improvement does not take place after a fair trial of medical treatment, and when an active process elsewhere can be ruled out. For the last seven years Mixter has been introducing from 300 to 1,200 cm. of air after withdrawal of the fluid. Nineteen of forty-nine cases were treated in this way, and the results suggest that air injection may give more beneficial results than simple laparotomy. In treatment of the plastic type, operation is of no value save in meeting complications and emergencies as they arise. Hygienic treatment is of paramount importance. Surgery should only aid and never supplant it.

Brauer,[142] in discussing the surgical treatment of pulmonary tuberculosis in children, says the only procedure to be considered is artificial pneumothorax. The tendency of the disease to become generalized, the preponderance of hilum lesions, and of hepatization must be borne in mind, when the disease is considered in connection with children. Hepatization does not respond well to this method of treatment, and only when the hilum process has spread to involve extensive areas of the lung is there any prospect of benefit.

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141. Mixter, C. G.: Boston M. & S. J. **185**:557 (Nov. 10) 1921.
142. Brauer, L.: Ztschr. f. Tuberk. u. Heilstättenw. **34**:647 (Oct.) 1921.